(fosinopril sodium)

Pr MONOPRIL*

IN A CLASS BY ITSELF

The only phosphinic ACE inhibitor

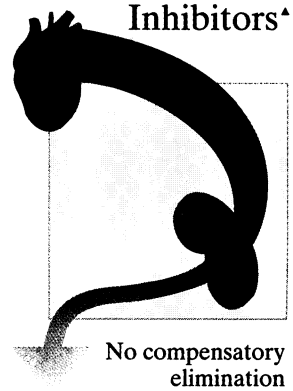
COMPENSATORY ELIMINATION: THE PATH TO SAFETY THE UNIQUE FACTOR

MONOPRIL'S UNIQUE SAFETY FACTOR MEANS:

- Less risk of drug accumulation[1]
- One simple 10 mg O.D. starting dose❤ is suitable for a wide range of hypertensive patients, regardless of race, age,‡ sex, hepatic or renal status[2]

MONOPRIL, taken once daily, offers proven 24-hour efficacy[2]

All other ACE Inhibitors▲



No compensatory elimination

Most frequent side effects may include a low incidence of headache, cough, and dizziness.

Before prescribing, please refer to prescribing information for the warning about use in pregnancy. ▲ Benazepril's dual route of elimination is not compensatory. † Monopril is indicated in the treatment of mild-to-moderate essential hypertension when diuretics or beta-blockers are unsuitable. ❤ Most patients have experienced 24-hour control on a single daily dose. ‡ The safety and efficacy of fosinopril in children have not been established.

References: **1.** Sica DA et al. Comparison of the steady-state pharmacokinetics of fosinopril, lisinopril, and enalapril in patients with chronic renal insufficiency. *Clin Pharmacokinet* 1991;20(5):420-427. **2.** Monopril Product Monograph.

NOW ON FORMULARY

Bristol-Myers Squibb
Pharmaceutical Group

PMAC PAAB

MON215F

Once-a-day

*Cardizem® CD

Controlled Delivery diltiazem HCl/MMDC

For angina

Cardizem® CD helps patients do whatever it is they've always loved to do.*[1]*

Performance from the Heart.

*Cardizem® CD is used as initial monotherapy to manage stable angina when nitrates or beta-blockers are inappropriate. Cardizem® CD offers a remarkable tolerability profile in angina patients, the most frequent side effects being headache (3%), dizziness (3%) and AV Block (5.8%).

Reference: 1. Product Monograph.

® Cardizem is a registered trademark of Marion Merrell Dow Inc., U.S.A.

MARION MERRELL DOW
CANADA

PMAB MEMBER PMAC

Without you, she may not know.

MONISTAT* *is a cure you can trust to treat vaginal yeast infections that can be caused by broad spectrum antibiotic therapy.*

You know that vaginal yeast infections can be triggered by some systemic antibiotics.[1] But your patients may not.

Forewarned they'll know that MONISTAT* can be applied at the first sign of a vaginal yeast infection.

MONISTAT* is a cure you know that can treat vaginal candidiasis based on nearly two decades of excellent efficacy with a proven safety margin.[2,3]

What's more, you can now recommend the new MONISTAT* 7-Day Combination Pack to treat difficult or recurrent yeast infections. It brings added flexibility to the convenient line of MONISTAT* products.

When you know that treating one problem can lead to another, tell your patients what to expect.

They trust you, and you know MONISTAT*.

MONISTAT*
MICONAZOLE NITRATE

TRUST A CURE YOU KNOW

In general complaints recorded with miconazole nitrate therapy concerned vulvovaginal burning, itching, irritation and edema and hives.

McNEIL McNEIL CONSUMER PRODUCTS COMPANY
Guelph, Canada N1K 1A5

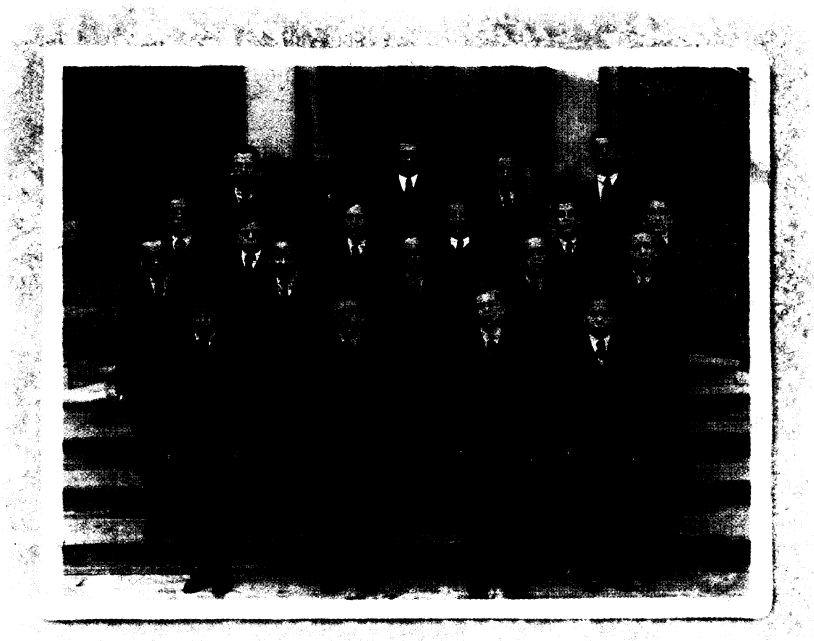
*Trademark © 1995

? 1 800 891-4857

References: 1. Sobel, JD. Vaginitis in Adult Women. Obstet Gynecol Clin North Am, 1990; 17(4):851-879.
2. Sobel JD. Individualizing treatment of vaginal candidiasis, J AM ACAD DERMATOL 1990;23:572-6. 3. American Hospital Formulary Service Drug Information, American Society of Hospital Pharmacists. 1994;p.2285.

PAAB CCPP

In the treatment of hypertension, some have the qualities to really stand out



LOZIDE, unlike many of the thiazide-type diuretics, effectively controls hypertension without significantly impairing glucose and lipid metabolism.[1-3]

As the only indoline diuretic,[2] LOZIDE stands in a class of its own. This leading diuretic,[§4] with widely proven efficacy, does not affect most metabolic parameters.*[2] (However, as with some other diuretics, it is recommended that serum potassium be determined at regular intervals and that potassium supplementation be instituted if required.[5])

Already provided in a 2.5-mg tablet, LOZIDE is now available in a 1.25-mg tablet, which gives you added dosage flexibility.

Offering the same efficacy as the 2.5-mg dose, this new 1.25-mg dose also helps minimize certain adverse effects,[2,3] thus better meeting the needs of your hypertensive patients.†

NEW LOZIDE 1.25 mg

Regardless of the dose you prescribe, you can be confident that LOZIDE provides your patients with these important therapeutic benefits:

- no observed adverse effects on L.V.H.;[6-9]
- flexible use as a single agent or in combination;
- once-a-day dosage for easy compliance.

For first-line treatment of essential hypertension with minimal risk of compromising your patients' lipid and glucose profiles, put your trust in the diuretic that sets itself apart.

Prescribe LOZIDE.

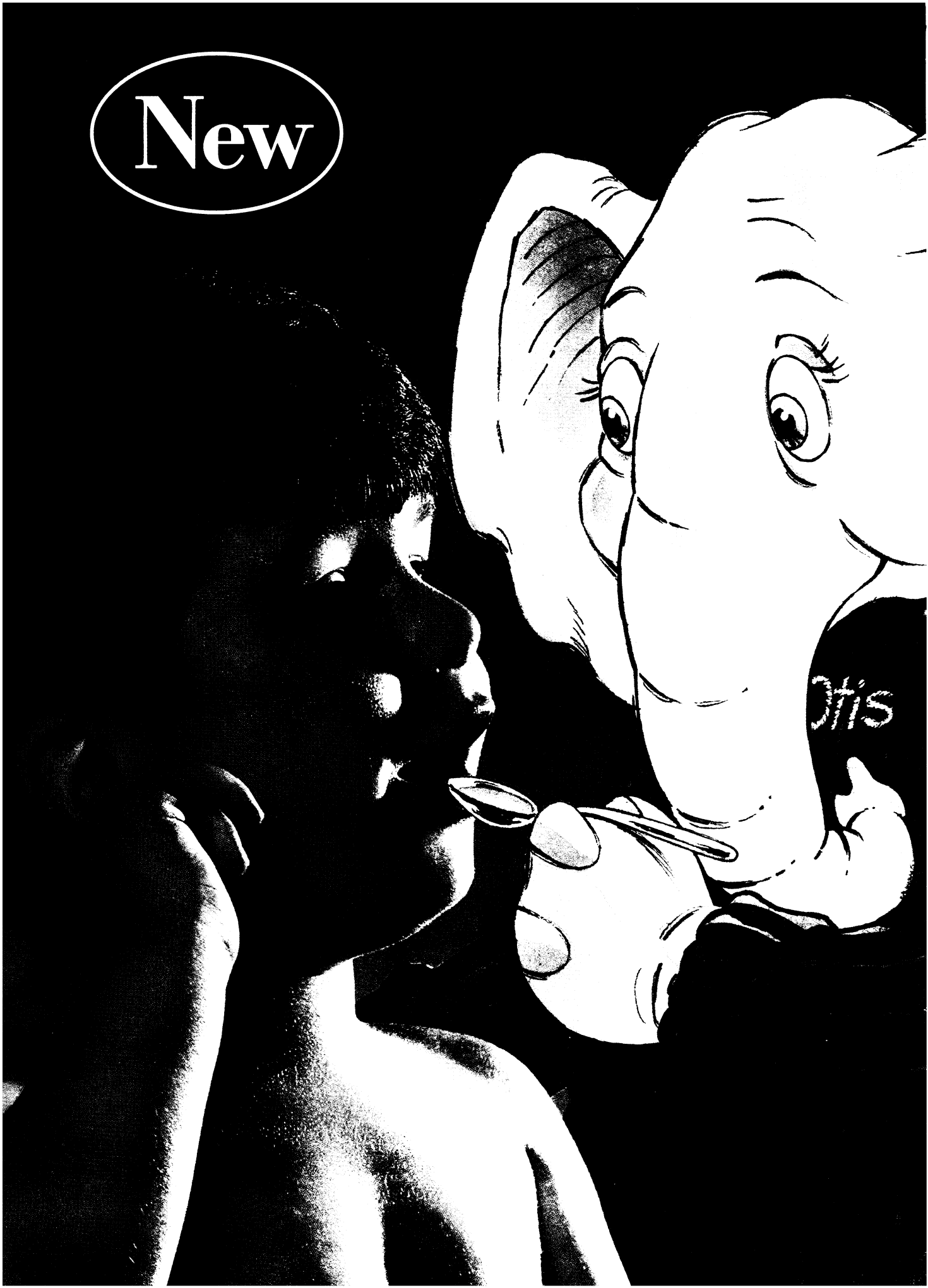
§ Based on *Canadian drugstore and hospital purchases*, IMS Canada, August 1995.
*Although LOZIDE exerts minimal effect on glucose metabolism, insulin requirements may be affected in diabetics and hyperglycemia and glycosuria may occur in patients with latent diabetes.
†Patients with renal insufficiency should be carefully monitored. ® Registered trademark.

SERVIER
Servier Canada Inc.
Laval (Quebec) Canada
H7V 4A7

PAAB CCPP

MEMBER PMAC ACIM

LOZIDE®
(Indapamide)
In a class of its own
The only indoline diuretic


New
Otis

Success story of the ear

And many ears to come!

Introducing Cefzil

- Greater *in vitro* activity than PrCeclor® against *S. pneumoniae* and *H. influenzae*, including resistant strains.[1†]
- Unlike Ceclor, Cefzil *is* indicated in *M. catarrhalis*.[2]
- Unlike Ceclor, Cefzil is effective *in vitro* against intermediate penicillin-resistant strains of pneumococci commonly present in middle ear fluid.[3,4]
- Excellent clinical success rates — up to 97% in otitis media.[5††]
- Very low rate of GI side effects (less than 3%) in both adults and children.[2]
- Great tasting bubble gum flavour suspension available, as well as tablets.
- Convenient twice-a-day dosage in otitis media for children‡ (15 mg/kg BID).
- Competitively priced compared to other oral cephalosporins.

and

- The Otis Compliance Kit™ — loads of fun for loads of compliance.

Prescribe a highly effective oral cephalosporin with confidence: Cefzil tablets or suspension indicated for otitis media caused by *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*.

† *In vitro* data. Not necessarily representative of clinical results.
†† Clinical success defined as resolution or improvement of signs and symptoms of infection with no new signs or symptoms emerging (n=122).
‡ Six months and older.

PrCeclor® (cefaclor) is a registered trademark of Eli Lilly Canada Inc.

Bristol-Myers Squibb
Pharmaceutical Group

*TM Authorized User Bristol-Myers Squibb Canada Inc.

PAAB | PMAC member

Pr cefzil*

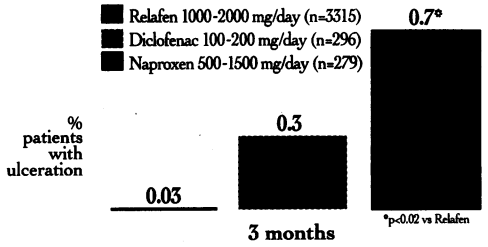
Success ear after ear

For prescribing information see page 593

"I was designed to do one thing very well, and one thing only. What am I?"

RELAFEN. AN NSAID DESIGNED TO RELIEVE ARTHRITIS, WITH FEWER ULCERS.

LESS ULCERATION THAN DICLOFENAC OR NAPROXEN[1]



Annual ulcer incidence with Relafen is far below the US Food and Drug Administration's reported range of 2-4% in chronic NSAID use.[2]

AS EFFECTIVE AS DICLOFENAC, NAPROXEN AND INDOMETHACIN IN OA AND RA[3,4]

Generally well tolerated, with fewer withdrawals due to GI side effects than diclofenac SR (14% vs 23%; upper abdominal pain p<0.04, dyspepsia p=0.01).[5]

Chart adapted from Eversmeyer W, Poland M et al.

SB SmithKline Beecham Pharma

SELECTIVE METABOLISM ELIMINATES 2 OUT OF 3 ROUTES OF ULCERATION

In vitro studies have shown that Relafen, a nonacidic prodrug, has no direct topical effect on the protective gastric mucosa,[6,7] and no indirect topical effect via bile reflux.[8,9,10†] And the active metabolite is only a weak inhibitor of protective gastric prostaglandins in vitro and ex vivo.[7]

For full information on precautions, warnings and contraindications please read the product monograph. †The clinical significance of in vitro data has not been established.

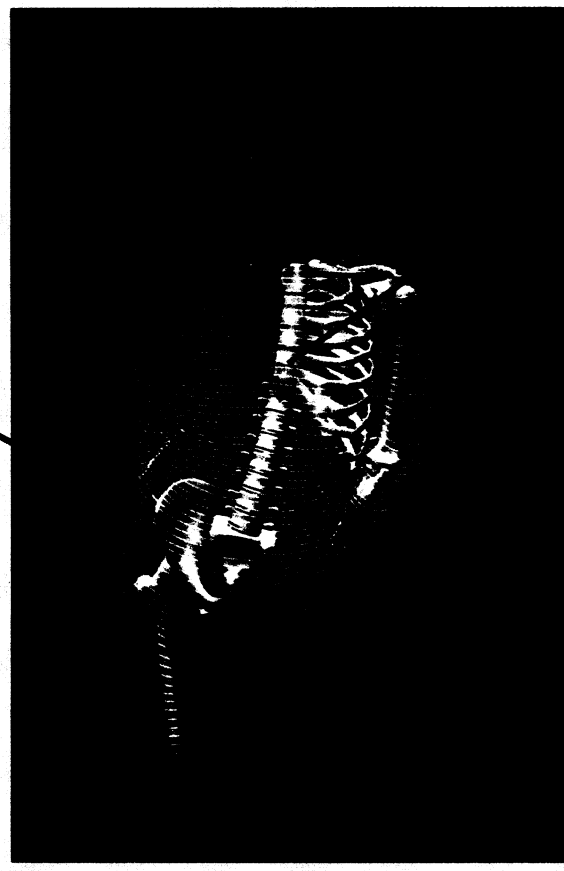
The implement above was precisely designed to perform one selective task – until the end of the nineteenth century, a tongue-scraper was an oral-hygiene must for the European well-to-do.

ONCE-A-DAY
RELAFEN
NABUMETONE

ACTIVE IN THE JOINTS, WITHOUT BEING ACTIVATED IN THE GI TRACT

What would a major advancement mean in the treatment of osteoporosis?

New PrFOSAMAX® increases bone mass in postmenopausal women



8.8% increase in BMD at the spine[1,**,†,‡]

7.8% increase in BMD* at the hip[1,†,‡]

3.1% increase in BMD at the wrist (ultradistal forearm)[2,†,‡]

20% of bone mass has been lost by the average postmenopausal woman

FOSAMAX® is a bone metabolism regulator.

FOSAMAX® is indicated for the treatment of osteoporosis in postmenopausal women.

* Bone Mineral Density

** In clinical studies, over 96% of patients studied for up to three years had a measured increase in spine BMD.[1]

† FOSAMAX® 10 mg daily produced statistically significant and clinically important increases in BMD at the hip, spine, and wrist (ultradistal forearm) relative to placebo at three years ($p \leq 0.001$).[1,2]

‡ Combined data from two large, identically designed, double-blind, placebo-controlled, three-year multicenter studies in 994 women with osteoporosis, defined as low bone mass, 397 received placebo and 196 of whom received FOSAMAX® 10 mg/day. To ensure an adequate calcium intake, all patients were supplemented with 500 mg of calcium per day.[1]

1. Liberman UA et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. N Engl J Med 1995;333(22):1437-43.

2. Data on file, Merck Frosst Canada Inc.: Two double-blind, randomized, placebo-controlled, parallel-group, multicenter studies to evaluate the safety and effect on bone density of daily oral MK-217 for two years in osteopenic postmenopausal women, with a one-year open treatment extension [Protocol No. 035 (US) and 037 (International)]-Three Year Data.

Builds bone to build independence

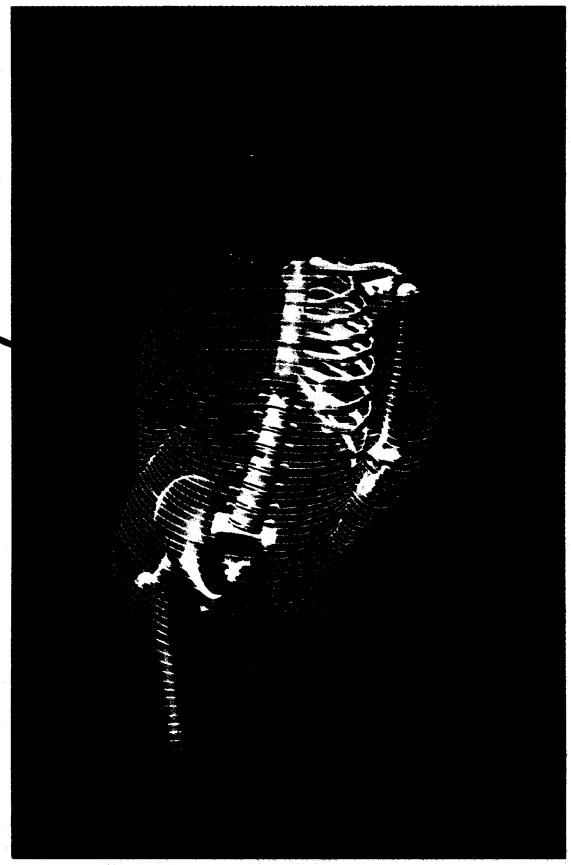
FOSAMAX®

alendronate sodium

New FOSAMAX® reduces the risk of vertebral fractures

48%

reduction in the proportion of patients treated with FOSAMAX® experiencing one or more vertebral fractures relative to those treated with placebo in pooled analysis (5-20 mg) (p=0.034)[1,¶]



Low bone mass is a major predictor of increased risk of osteoporotic fractures[3]

¶ Vertebral fractures occurred in 6.2% (22/355) of patients who received placebo and 3.2% (17/526) of patients who received FOSAMAX® (5 or 10 mg for 3 years or 20 mg for 2 years followed by 5 mg for 1 year).[1]

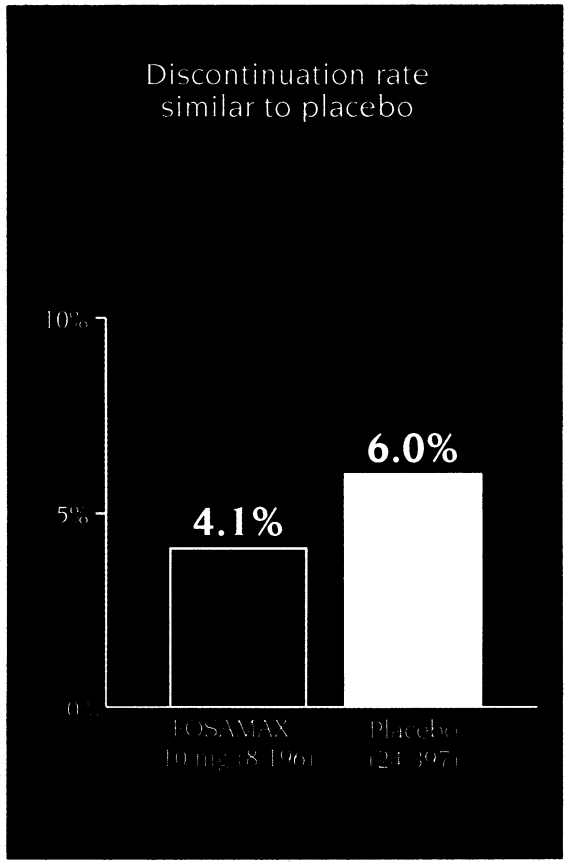
3. Consensus Development Conference: Diagnosis, prophylaxis, and treatment of osteoporosis. Am J Med 1993;94:646-9.

Builds bone to build independence

FOSAMAX®

alendronate sodium

New FOSAMAX®
generally well tolerated
nonhormonal therapy



Adapted from the product monograph

- ▶FOSAMAX® has been evaluated for safety in clinical studies in 994 postmenopausal patients.
- ▶The overall safety profiles of FOSAMAX® 10 mg per day and placebo were similar.
- ▶Adverse events were usually mild and generally did not require discontinuation of therapy.

As with other bisphosphonates, caution should be used when FOSAMAX® is given to patients with active upper gastrointestinal problems, such as dysphagia, symptomatic esophageal diseases, gastritis, duodenitis, or ulcers.

FOSAMAX® is contraindicated in patients who are hypersensitive to any component of this product, patients who are hypocalcemic, or patients who suffer from renal insufficiency (creatinine clearance < 35 mL/min).

Builds bone to build independence

FOSAMAX®
alendronate sodium

MERCK FROSST

BEFORE PRESCRIBING, PLEASE CONSULT THE PRESCRIBING INFORMATION.

MERCK SHARP & DOHME CANADA
DIV. OF MERCK FROSST CANADA INC.
KIRKLAND, QUEBEC

PAAB

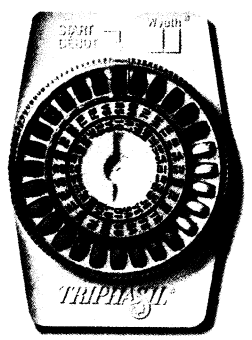
FSM-96-CDN-9410-JA

CONfIDENCE

IT'S SOMETHING THAT'S BUILT OVER TIME

And it's what we want you and your patients to have. For over 12 years,[1] Triphasil Cyclette has been providing reliable contraception to Canadian women.

Triphasil offers an approach to contraception that reflects the phases of a woman's natural cycle.[2] The result is excellent cycle control, with a low incidence of side effects.*[3,4]



With over 3.5 million patient-years of use in Canada,[1] Triphasil Cyclette offers the clinical experience to help you prescribe an O.C. with confidence.[1,4] It's a good feeling. For you and your patients.

For more information about confidence in Triphasil call 1-800-511-9666.

*As with all O.C.s, patients should be properly selected and followed-up regularly. Please refer to the product monograph for detailed safety information.

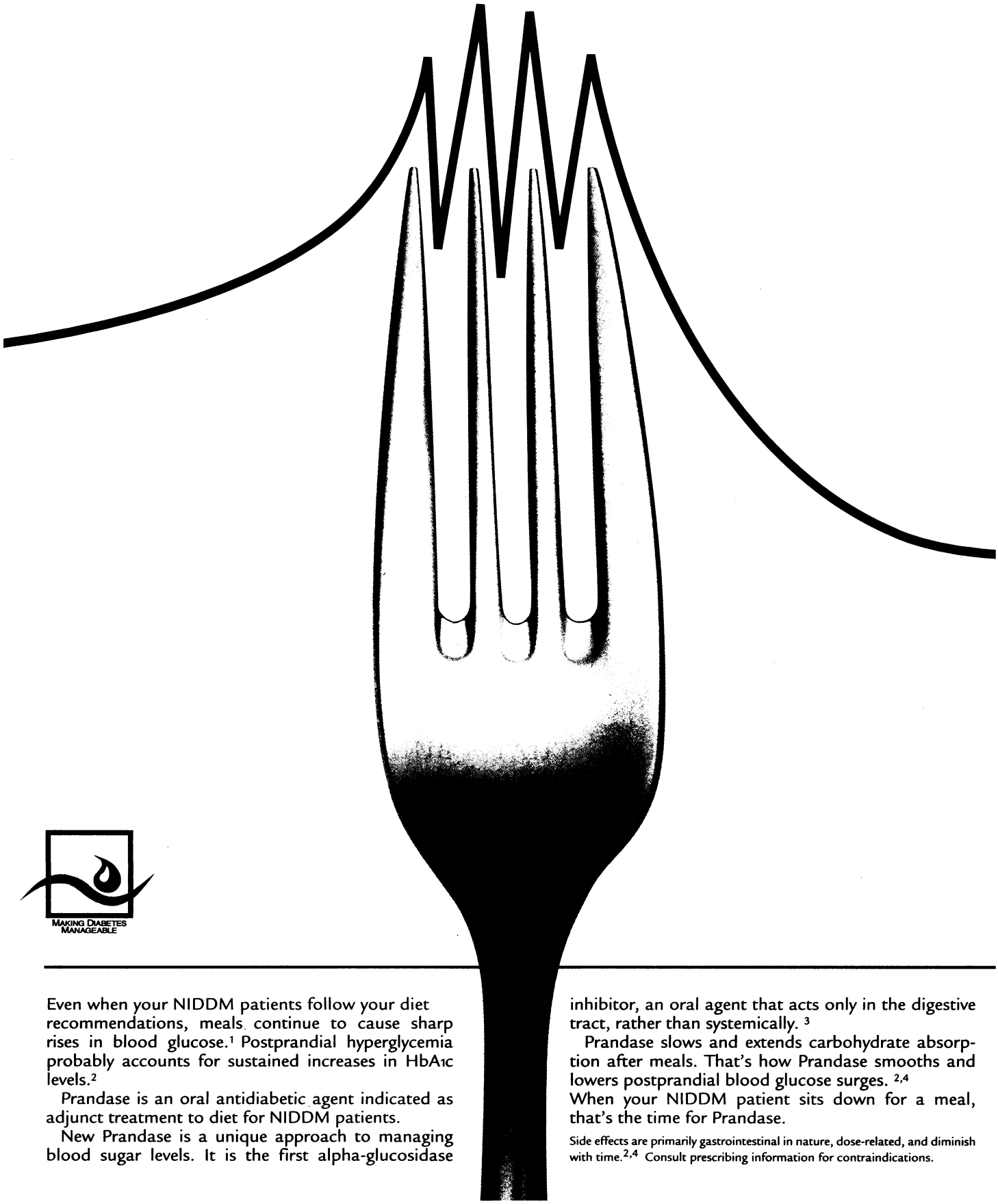
levonorgestrel and ethinyl estradiol

TRIPHASIL Cyclette

CANADA'S MOST PRESCRIBED ORAL CONTRACEPTIVE

WYETH-AYERST CANADA INC.
Montreal, Canada H4R 1J6

In NIDDM patients, blood levels surge after meals.



MAKING DIABETES MANAGEABLE

Even when your NIDDM patients follow your diet recommendations, meals continue to cause sharp rises in blood glucose.[1] Postprandial hyperglycemia probably accounts for sustained increases in HbA1c levels.[2]

Prandase is an oral antidiabetic agent indicated as adjunct treatment to diet for NIDDM patients.

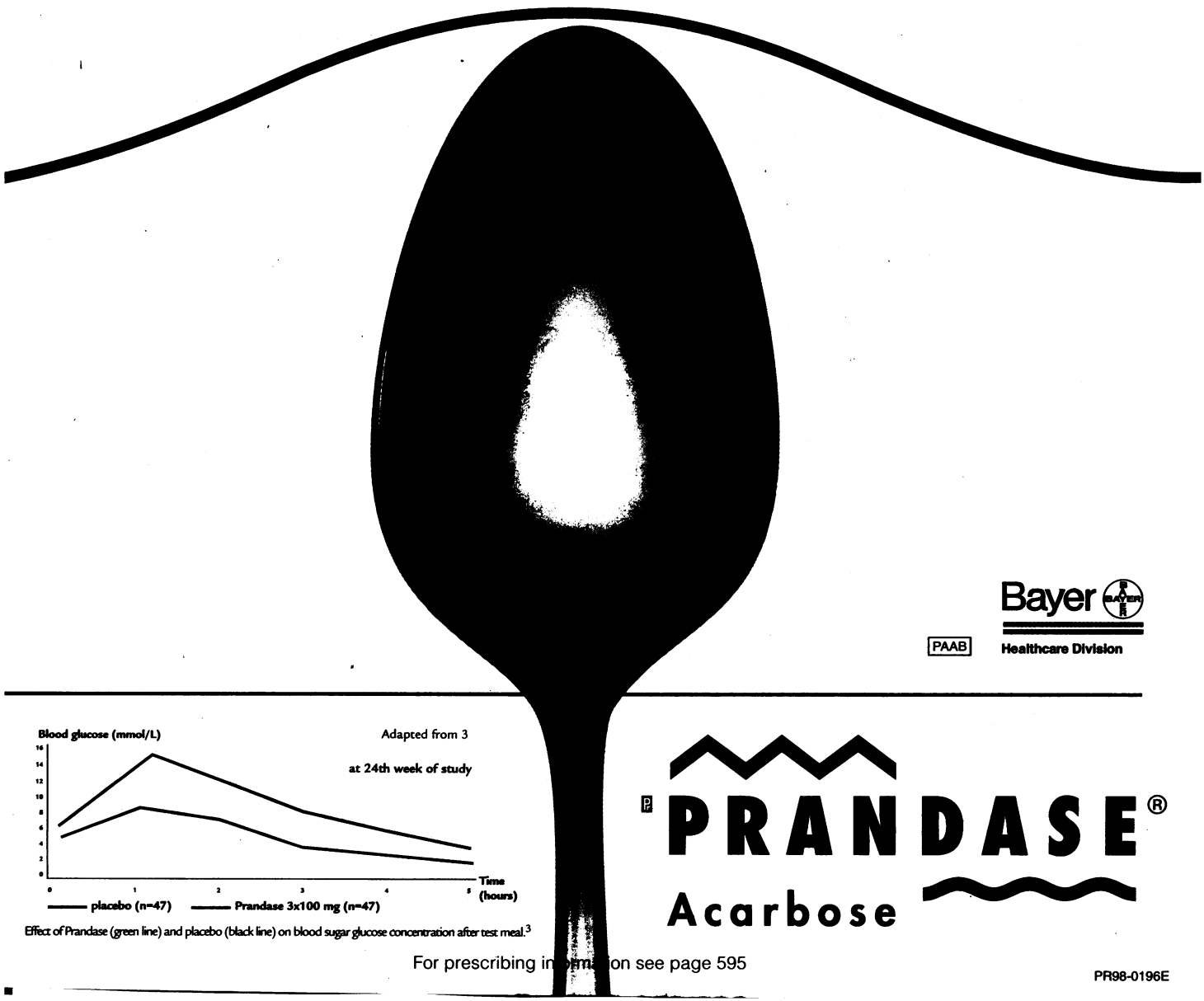
New Prandase is a unique approach to managing blood sugar levels. It is the first alpha-glucosidase inhibitor, an oral agent that acts only in the digestive tract, rather than systemically.[3]

Prandase slows and extends carbohydrate absorption after meals. That's how Prandase smooths and lowers postprandial blood glucose surges.[2,4]

When your NIDDM patient sits down for a meal, that's the time for Prandase.

Side effects are primarily gastrointestinal in nature, dose-related, and diminish with time.[2,4] Consult prescribing information for contraindications.

New PRANDASE smooths and lowers the sharp points



Bayer
PAAB Healthcare Division

Adapted from 3

at 24th week of study

Effect of Prandase (green line) and placebo (black line) on blood sugar glucose concentration after test meal.[3]

PRANDASE®

Acarbose

For prescribing information see page 595

PR98-0196E

As comforting as new Pediatric Biaxin.

Bringing success in adult RTI to Acute Otitis Media.

The special pediatric formulation of Biaxin offers the comfort of proven clinical success in acute otitis media,[1-4] with effective coverage against typical, atypical and beta-lactamase-producing respiratory pathogens.[5*]

Along with many other comforts for your little patients. A good side effect profile,[5†] with *no cross allergenicity* with penicillins, cephalosporins or sulfonamides.[‡] The convenience of b.i.d. dosing.[5] And the good taste of wild berry flavour.

Of course, Pediatric Biaxin could be more comforting if it were also warm and fuzzy. We're working on it.

* Indicated for Acute Otitis Media caused by *H. influenzae, M. catarrhalis, or S. pneumoniae* and mild to moderate community-acquired pneumonia caused by *S. pneumoniae, C. pneumoniae, or M. pneumoniae.*

† Most commonly reported adverse events in the digestive system were diarrhea (7%), vomiting (7%), abdominal pain (3%) and nausea (1%).

‡ Biaxin is contraindicated in patients with a known hypersensitivity to clarithromycin, erythromycin or other macrolide antibacterial agents.

ABBOTT COMMITTED TO THE CONQUEST OF INFECTIOUS DISEASE

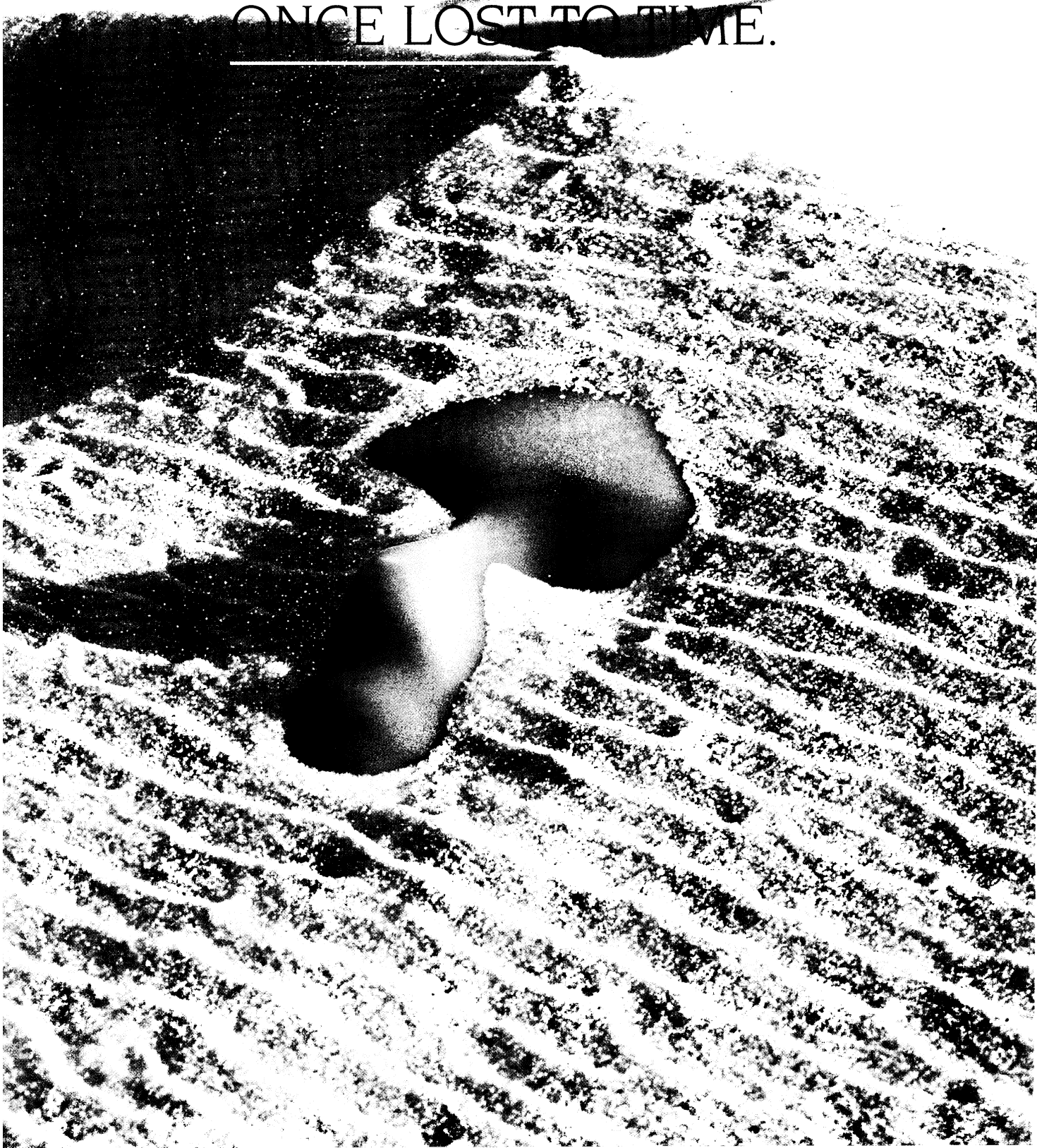
Product Monograph available on request. 1-KAH

Pediatric Pr BIAXIN® NEW

CLARITHROMYCIN SUSPENSION

Comfort for little patients.

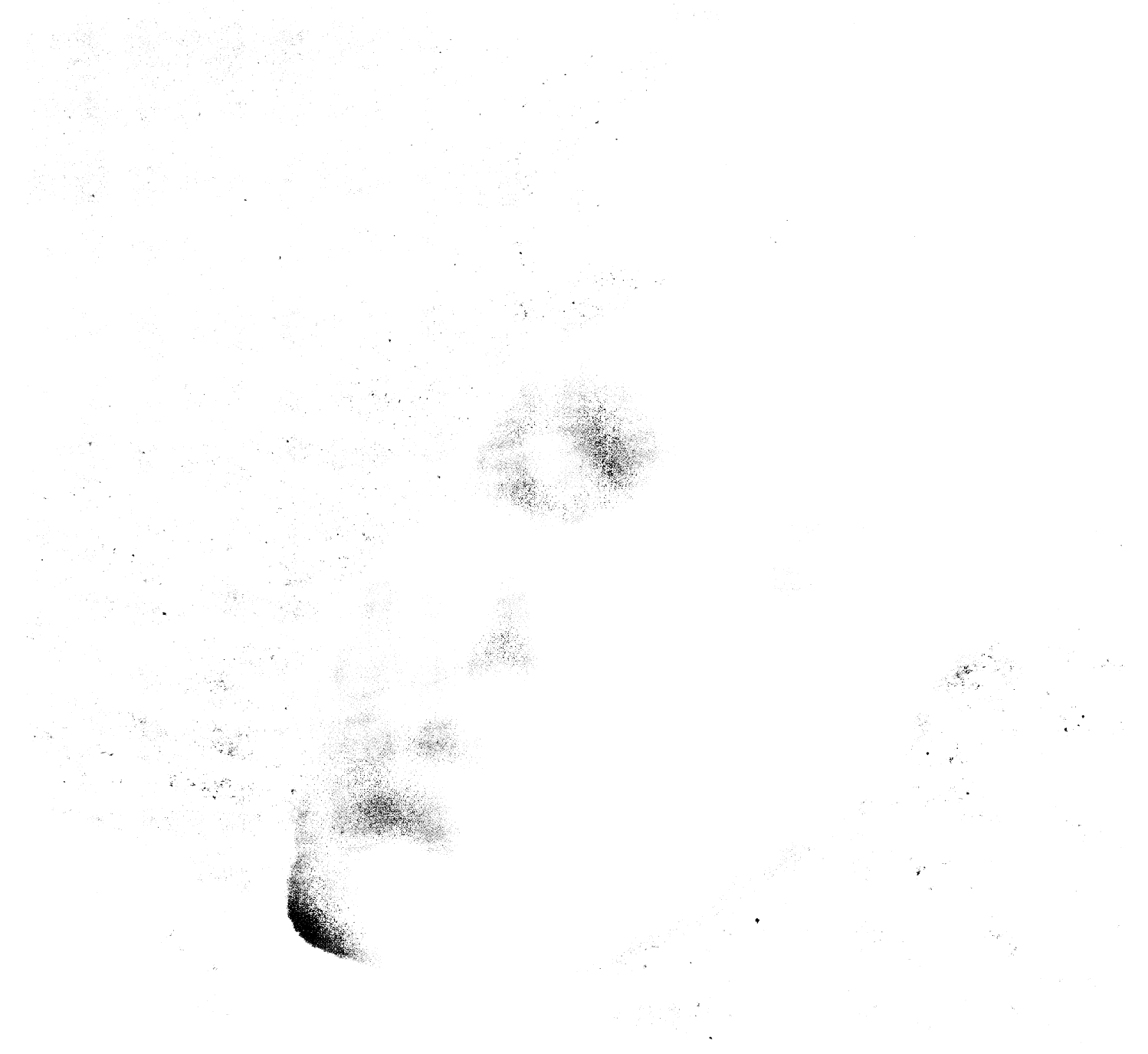
A NEW WAY TO REVEAL THE BEAUTY ONCE LOST TO TIME.



INTRODUCING NEW

Pr RENOVA*

tretinoin emollient cream 0.05%



ONLY THE PICTURES CAN TELL THE STORY.

Fine lines - periorbital

Baseline

Week 24[4]

Mottled hyperpigmentation (brown spots)

Baseline

Week 24[4]

THE FIRST TRETINOIN THERAPY SPECIFICALLY FORMULATED TO REVERSE THE EFFECTS OF SUN AND TIME

Now, you can offer your patients the benefits of the first tretinoin therapy specifically formulated to repair the effects of sun and time. New RENOVA* 0.05% emollient cream was proven to be the optimal formulation among prototypes tested for treatment of photodamage.[3] Unlike most cosmetics, RENOVA 0.05% emollient cream actually improves the skin's underlying structure.[1,2] The unique emollient cream base was created especially for dry, mature skin.[9]

Complexion visibly improved in most patients after six months: fine wrinkles improved in 79% of patients,[†4] while mottled hyperpigmentation decreased in 63% of patients.[††3] Moreover, side effects (including peeling/dry skin, burning/stinging, pruritus/erythema) tended to be mild and decrease with time (only 2.5% of patients withdrew due to adverse reactions).[3]

And only RENOVA 0.05% emollient cream offers the RENOVA Skin Therapy Program, a unique, comprehensive program designed to offer patients both support and information on skin care and general health. As part of a comprehensive skin protection program, patients should wear a sunscreen (minumum SPF of 15) and protective clothing.

To learn more about RENOVA 0.05% emollient cream, call 1-800-449-6864.

Unretouched photos under standard lighting from clinical trials of RENOVA 0.05% emollient cream. Individual results may vary.
[†]n=31; p<0.001. [††]n=76; p=0.010. NOTE: RENOVA 0.05% emollient cream should not be used by women who are pregnant or lactating. RENOVA 0.05% emollient cream should be applied once nightly, to lightly cover the entire face.

Pr RENOVA*

tretinoin emollient cream 0.05%

PRESCRIBING INFORMATION.

NAME OF DRUG
RENOVA
tretinoin emollient cream 0.05%
PHARMACOLOGIC CLASSIFICATION
Agent for the treatment of photodamaged skin
ACTIONS, CLINICAL PHARMACOLOGY
RENOVA tretinoin emollient cream 0.05% significantly reduces clinical signs of photodamaged skin such as fine wrinkles, mottled hyperpigmentation and roughness. While the exact mechanism of action of RENOVA emollient cream 0.05% is unknown, the clinical improvements are accompanied by the following histologic changes: increased epidermal and granular layer thickness, reduced melanin content and stratum corneum alterations.
INDICATIONS AND CLINICAL USE
RENOVA tretinoin emollient cream 0.05% is indicated for the treatment of fine wrinkling, mottled hyperpigmentation, and roughness of the skin. These signs are usually associated with photodamaged (sun-damaged) skin and intrinsic aging, but may be associated with other conditions.
The safety and efficacy of RENOVA emollient cream 0.05% for the prevention or treatment of actinic or solar keratoses have not been established.
CONTRAINDICATIONS
RENOVA tretinoin emollient cream 0.05% is contraindicated in individuals with a history of sensitivity reactions to any of its components. It should be discontinued if hypersensitivity to any of its ingredients is noted.
WARNINGS
RENOVA tretinoin emollient cream 0.05% should be used under medical supervision as part of a comprehensive skin protection program, including use of sunscreen products and protective clothing. Excessive use of RENOVA emollient cream 0.05% should be avoided. RENOVA emollient cream 0.05% should be kept away from the eyes, mouth, angles of the nose or mucous membranes. Topical use may induce severe local erythema, pruritus, burning or stinging and peeling at the site of application. If the degree of local irritation warrants, patients should be directed to use the medication less frequently, discontinue use temporarily, or discontinue use altogether.
Tretinoin has been reported to cause severe irritation on eczematous skin and should be used with utmost caution in patients with this condition.
Use in Pregnancy
Topical tretinoin should be used by women of childbearing years only after contraceptive counselling. It is recommended that topical tretinoin should not be used by pregnant women.
There have been a few reports of birth defects among babies born to women exposed to *topical* tretinoin during pregnancy. To date, there have been no adequate and well-controlled prospective studies performed in pregnant women and the teratogenic blood level of tretinoin is unclear. However, a retrospective cohort study of babies born to women exposed to topical tretinoin during the first trimester of pregnancy found no excess birth defects among these babies when compared with babies born to women in the same cohort who were not similarly exposed.
Oral tretinoin has been shown to be teratogenic and fetotoxic in rats when given in doses 1000 and 500 times the topical human dose, respectively.
In nine (9) out of ten (10) *topical* teratology studies of tretinoin conducted in rats and rabbits using several formulations, there has been no evidence of teratogenicity. In one (1) out of ten (10) studies, there was an increase in fetal malformations; however, a clear causal relationship of topical tretinoin and these findings could not be established. In a repeat of this study, there were no fetal malformations. Topical tretinoin can produce treatment-related fetal effects (delayed ossification of bones and an increase in supernumerary ribs). The fetal no effect dose is 1.0 mg/kg/day (200 times the recommended clinical dose). [See **TOXICOLOGY - Reproduction and Teratology** subsection].
Nursing Mothers
It is not known whether tretinoin is excreted in human milk. Nevertheless, a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the importance of the drug to the mother.
Pediatric Use
Safety and effectiveness in children have not been established.
PRECAUTIONS
GENERAL
If a reaction suggesting sensitivity, chemical irritation, or a systemic adverse effect should occur, use of RENOVA tretinoin emollient cream 0.05% should be discontinued.
Exposure to sunlight, including sunlamps, should be avoided or minimized during the use of RENOVA emollient cream 0.05% and patients with sunburn should be advised not to use the product until fully recovered because of heightened susceptibility to sunlight as a result of the use of tretinoin. **Patients who may be required to have considerable sun exposure due to occupation and those inherently sensitive to the sun should exercise particular caution. Use of sunscreen products and protective clothing over treated areas is recommended when exposure cannot be avoided.** Weather extremes, such as wind or cold, also may be irritating to patients under treatment with tretinoin.
Carcinogenesis
The mutagenic potential of tretinoin was evaluated in the Ames assay and the *in vivo* mouse micronucleus assay, both of which were negative. In a life-time study of topical tretinoin in CD-1 mice, there was no evidence of carcinogenic potential. Studies in hairless albino mice suggest that tretinoin may accelerate the tumorigenic potential of weakly carcinogenic light from a solar simulator. Although the significance of these studies to man is not clear, patients should avoid or minimize exposure to sun.
Information for Patients
A patient information leaflet has been prepared and is included with each package of RENOVA emollient cream 0.05% (See Patient Package Insert section for text). The skin of certain sensitive individuals may become excessively red, swollen, blistered, or crusted. RENOVA emollient cream 0.05% should be discontinued if patients experience severe or persistent irritation, and they should be advised to consult their physician.
Drug Interactions
Concomitant topical medication, medicated or abrasive soaps, shampoos and cleansers, cosmetics that have a strong drying effect, and products with high concentrations of alcohol, as well as astringents and products that may irritate the skin, should be used with caution because they may increase irritation with RENOVA emollient cream 0.05%.
ADVERSE REACTIONS
In double-blind, vehicle-controlled studies involving 199 patients who received RENOVA tretinoin emollient cream 0.05% for facial photodamage, adverse reactions associated with the use of RENOVA emollient cream 0.05% were limited primarily to the skin. Local reactions such as peeling or dry skin, burning or stinging, erythema, and pruritus were reported by most subjects during therapy with tretinoin emollient cream. These signs and symptoms were usually of mild to moderate severity and were generally well-tolerated. These skin reactions occurred early in therapy and, except for dryness and peeling which tended to persist during therapy, generally decreased over the course of therapy.
SYMPTOMS AND TREATMENT OF OVERDOSAGE
RENOVA tretinoin emollient cream 0.05% is indicated for topical use only. If medication is applied excessively, no more rapid or better results will be obtained and marked redness, peeling, or discomfort may occur. Oral ingestion of this drug may lead to the same side effects as those associated with excessive oral intake of Vitamin A.
DOSAGE AND ADMINISTRATION
RENOVA tretinoin emollient cream 0.05% should be applied once daily at bedtime, to lightly cover the entire face. In some cases it has been necessary to temporarily discontinue therapy or to reduce the frequency of application. When the patient is able to tolerate the treatment, therapy can be resumed or the frequency of application can be increased.
Improvement in facial photodamage with RENOVA emollient cream 0.05% treatment occurs gradually over the course of therapy. Six months of therapy may be required before definite beneficial effects are seen.
Patients treated with RENOVA emollient cream 0.05% should use an effective sunscreen with a minimum SPF of 15 as well as protective clothing when exposure to the sun cannot be avoided.
PHARMACEUTICAL INFORMATION
RENOVA tretinoin emollient cream 0.05% contains the active ingredient tretinoin, a retinoid. Tretinoin appears as a yellow to light orange crystalline powder having a characteristic odour. Tretinoin is soluble in dimethyl sulfoxide, slightly soluble in polyethylene glycol 400, octanol, and ethanol (100%), practically insoluble in water and mineral oil, and insoluble in glycerin. The chemical names for tretinoin are retinoic acid and all-*trans*-retinoic acid (MW = 300.44).
RENOVA emollient cream 0.05% is available at a concentration of 0.05% w/w in a formulation of light mineral oil, sorbitol solution, hydroxyoctacosanyl hydroxystearate, methoxy PEG-22/dodecyl glycol copolymer, PEG-45/dodecyl glycol copolymer, stearoxytrimethyl-silane and stearyl alcohol, dimethicone 50cs, fragrance, methylparaben, edetate disodium, quaternium-15, butylated hydroxytoluene, citric acid (monohydrate) and purified water.
Store between 15°C and 25°C. DO NOT FREEZE.
AVAILABILITY
RENOVA tretinoin emollient cream 0.05% is a yellow cream having a characteristic floral odour. The cream contains 0.5 mg tretinoin per gram and is available in tubes containing 20 and 40 grams.
RENOVA emollient cream 0.05% is a prescription drug (Schedule F).
Full product monograph available to physicians and pharmacists upon request.
REFERENCES:
1. Gardner SS, Weiss JS. Clinical features of photodamage and treatment with topical tretinoin. *J Dermatol Surg Oncol* 1990;16:925-31. **2.** Griffiths CEM, Russman AN, Majmudar G, Singer RS, Hamilton TA, Voorhees JJ. Restoration of collagen formation in photodamaged human skin by tretinoin (retinoic acid). *N Engl J Med* 1993;329:530-5. **3.** Olsen EA, Katz HI, Levine N, Shupack J, Billys MM, Prawer S et al. Tretinoin emollient cream: a new therapy for photodamaged skin. *J Am Acad Dermatol* 1992;26:215-24. **4.** Data on File. Ortho-McNeil Inc. Protocol H87-064. **9.** RENOVA 0.05% emollient cream product monograph.

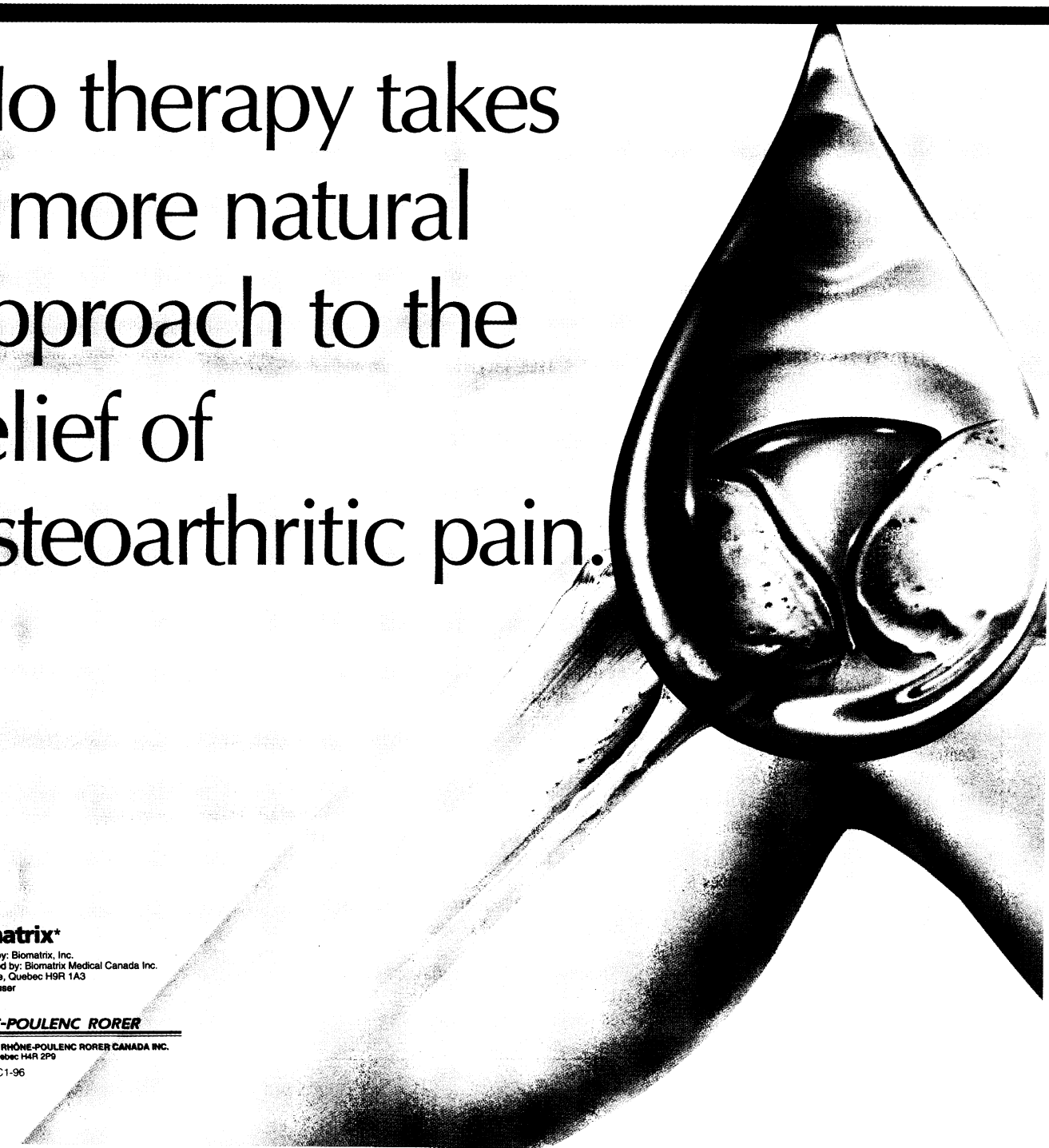
JANSSEN PHARMACEUTICA North York, Ontario
Distributed by Janssen Pharmaceutica Inc.

℞ RENOVA*

tretinoin emollient cream 0.05%

No NSAID.
No analgesic.
No corticosteroid.

No therapy takes a more natural approach to the relief of osteoarthritic pain.



Biomatrix*

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Manufactured by: Biomatrix Medical Canada Inc.
Pointe-Claire, Quebec H9R 1A3
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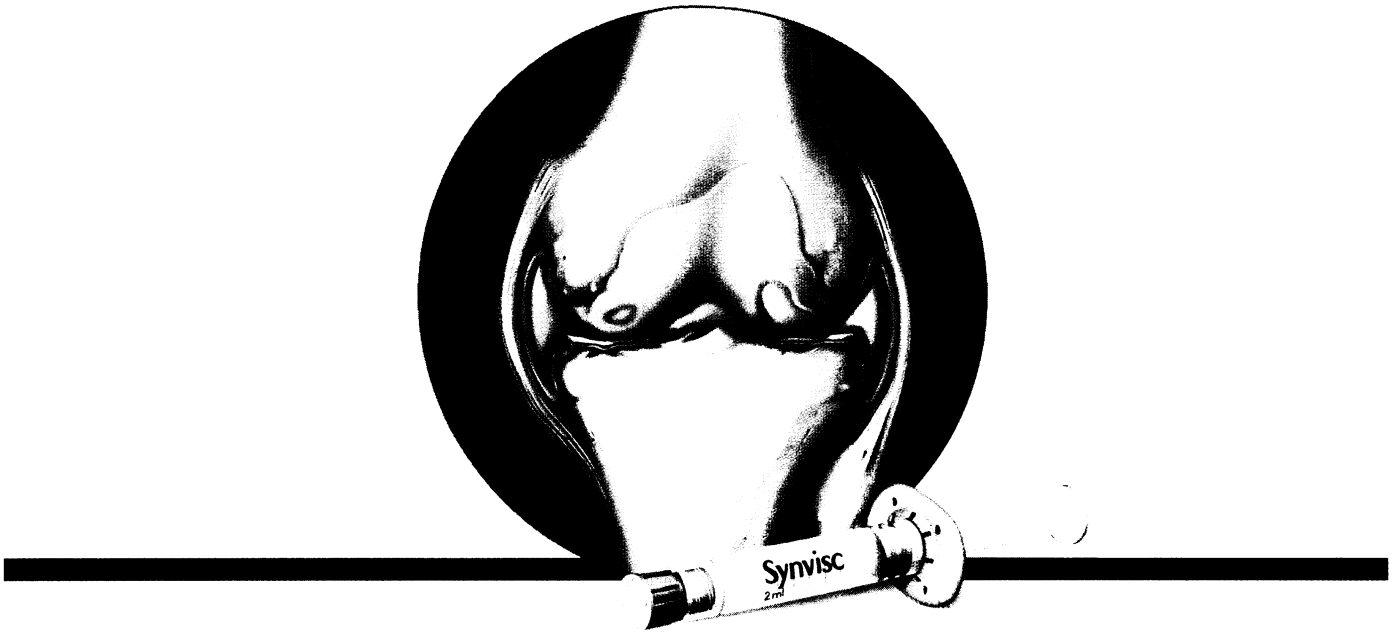

Safe, natural approach avoids the side effects of traditional therapies.

In the management of osteoarthritis of the knee, more and more Canadian physicians are introducing their patients to Synvisc. Safe, effective and natural, Synvisc is an appreciated alternative to NSAIDs, analgesics and corticosteroids.[1] Not only does Synvisc alleviate knee-joint pain,[1] it actually restores joint mobility.[2]

Made from slightly modified hyaluronan, a natural component of joint fluid; Synvisc produces none of the systemic problems common to traditional arthritis medications. No stomach pain. No nausea. No ulcers.[1] (Transient local pain and swelling in the injected knee may occur in some patients.)

Synvisc protects, absorbs shock and lubricates naturally, increasing joint flexibility.

Synvisc treats this source of discomfort directly, through a process called viscosupplementation.

This means that Synvisc, administered by injection into the painful joint, restores the natural viscosity and elasticity of the synovial fluid, which are diminished in osteoarthritis.[2]

In effect, Synvisc protects joint tissues, absorbs shock, and eases movement.[2]

Restores joint mobility for up to six months of increased comfort between treatments.

One course of treatment reduces pain significantly for up to six months or more[1] — facilitating movement[1] and enhancing the quality of everyday life.

So offer your osteoarthritic patients the relief they've been wishing for. Prescribe Synvisc. And restore normal joint function the natural way — *the safe way.*

References:
1. Adams, ME. An analysis of clinical studies of the use of crosslinked hyaluronan, hylan, in the treatment of OA. *J Rheumatol.* 1993;8;[20](suppl 39):16-18.
2. Balazs, EA, Denlinger, JL. Viscosupplementation: a new concept in the treatment of OA. *J Rheumatol.* 1993;8;[20](suppl 39):3-9.

Synvisc®

(hylan G-F 20)

Restores, protects, lubricates.

Eli Lilly Canada Inc.
Scarborough, Ontario

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PAAB CCPP

As with other SSRIs, the most commonly observed adverse events seen with Prozac were headache, nervousness, insomnia, drowsiness, fatigue, anxiety, tremor and dizziness. 15% of approximately 4,000 patients discontinued treatment because of side effects.

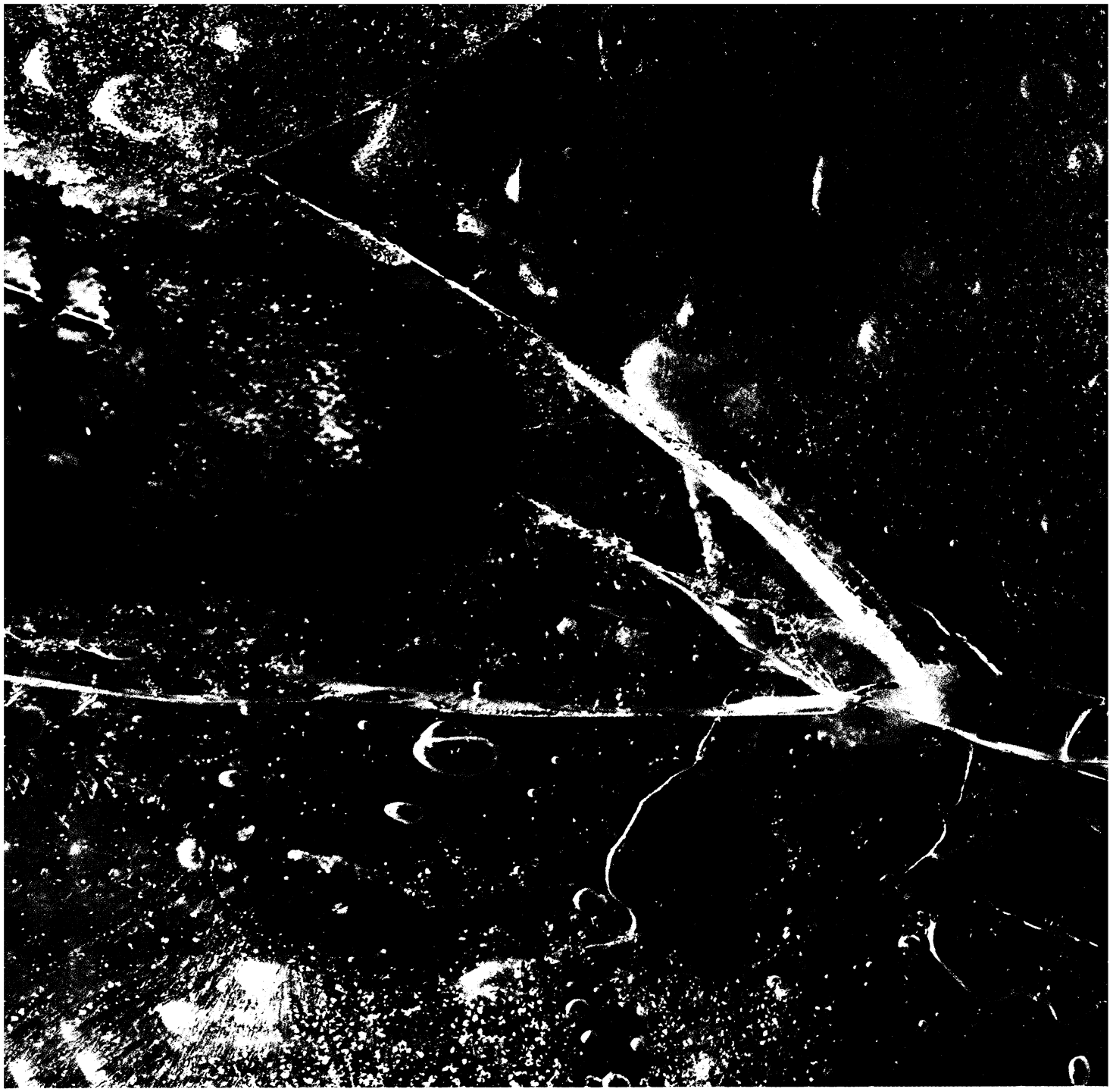
SELDOM HAS ONE DRUG HELPED CHANGE SO MANY LIVES

Pr PROZAC®
fluoxetine hydrochloride

AS YOUR FIRST LINE OF ACTION

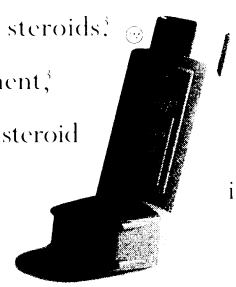
SELECTIVE SEROTONIN REUPTAKE INHIBITOR

TM Product appearance (colour, shape and size of capsule) is a trademark owned by Eli Lilly and Company and used under license. If 20 mg fluoxetine hydrochloride capsules look like this, patients can feel confident that they come from Eli Lilly and Company.



INTRODUCING FLOVENT®, WITH LESS

We understand there's a perception of risk associated with the long term use of inhaled steroids.[2] Now after 15 years of research and development,[3] Glaxo introduces a remarkable new inhaled steroid for the treatment of asthma. New *Flovent* (fluticasone propionate), with less than 1% oral systemic availability.[1-3]



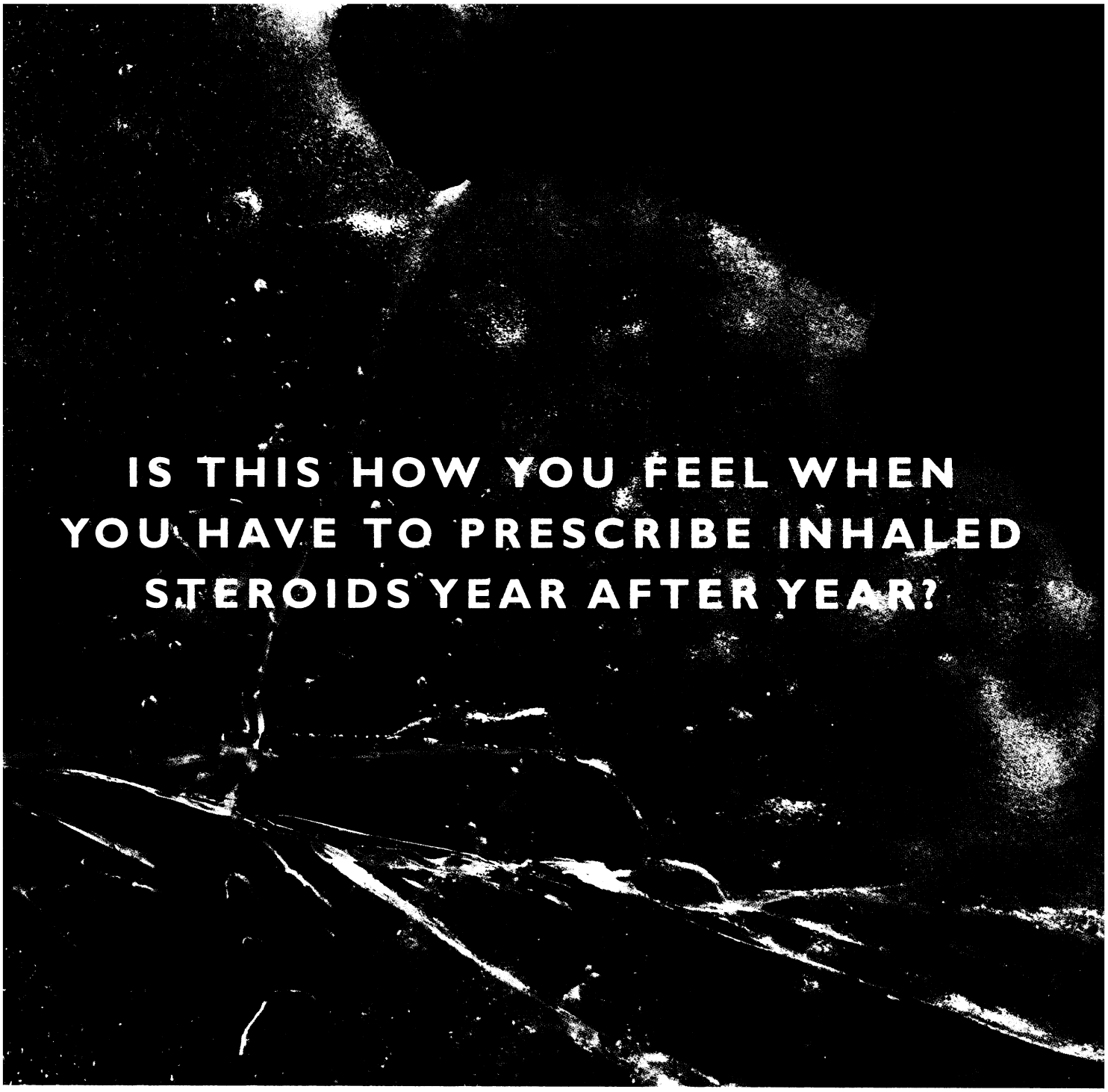
EXTENDING THE SAFETY MARGIN

Even at doses equivalent to 4000 mcg/day of *our own* [fa]Becloforte®* (beclomethasone dipropionate), adrenal function remains normal in adult asthmatics.[1,3]

And compared to Becloforte,[4] *Flovent* has consistently demonstrated a favourable safety

Flovent maximum daily adult dose is 2000 mcg, the equivalent of 4000 mcg of Becloforte.[1]

†Studies up to 12 months duration. The most common local side effects in adults and children are oropharyngeal candidiasis (3%) and hoarseness (2%).[1]



THAN 1% ORAL SYSTEMIC AVAILABILITY.[1,2]

profile over the short and long term.[5-9] *Flovent* has also established a safety and tolerability profile in children as young as four years old, with no evidence of adrenal suppression or effect on growth.[9-13]

NO COMPROMISE ON EFFICACY

In addition to this extended safety margin, *Flovent* offers *all* the efficacy you've come to expect from *our own* Becloforte.®[5-9] New *Flovent* therapy. With a safety profile suitable for the long term. For more information, please call 1-800-268-0324.

Flovent®

(fluticasone propionate inhaler)

Less than 1% oral systemic availability

Glaxo Wellcome Inc.

PAAB CCPP

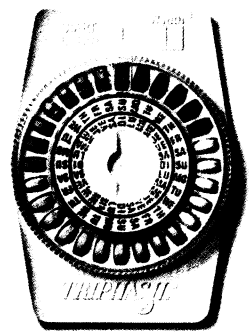
For prescribing information see page 602

TRUST

IT'S SOMETHING THAT'S EARNED OVER TIME

And it's what we want you and your patients to have. An oral contraceptive should offer reliable contraception, excellent cycle control, a low incidence of side effects and long-term use.[3,4]

Triphasil can provide these benefits,* and the Cyclette packaging helps make compliance easy and can reduce errors.



With over 12 years of use in Canada, for over 3.5 million patient-years of experience,[1] Triphasil Cyclette offers experience you can trust. Yours.

For more information about trust in Triphasil call 1-800-511-9666.

*As with all O.C.s, patients should be properly selected and followed-up regularly. Please refer to the product monograph for detailed safety information.

levonorgestrel and ethinyl estradiol

®TRIPHASIL Cyclette

CANADA'S MOST PRESCRIBED ORAL CONTRACEPTIVE

WYETH-AYERST CANADA INC.
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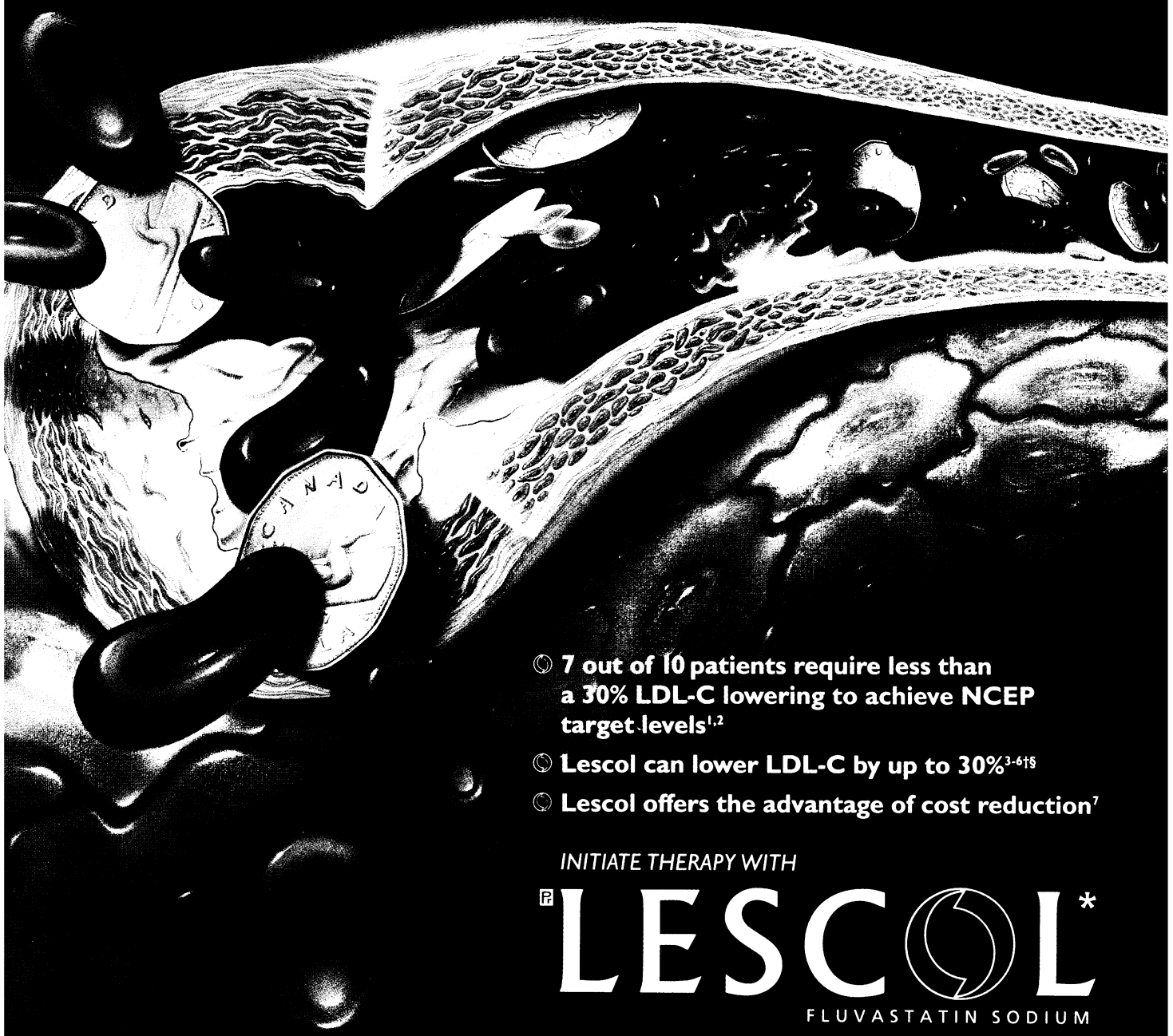
Can An HMG Be Too Rich For Their Blood?



- 7 out of 10 patients require less than a 30% LDL-C lowering to achieve NCEP target levels[1,2]
- Lescol can lower LDL-C by up to 30%[3-6†§]
- Lescol offers the advantage of cost reduction[7]

INITIATE THERAPY WITH

LESCOL*

FLUVASTATIN SODIUM

HMG$^{\Delta}$ efficacy made affordable[7]

$^{\Delta}$HMG-CoA reductase inhibitor.

†Lescol is indicated as an adjunct to diet in the treatment of elevated Total cholesterol (Total-C) and LDL-C levels in patients with primary hypercholesterolemia (types IIa and IIb) whose response to dietary restriction of saturated fat, cholesterol and other non-pharmacological measures have not been adequate.

§As with other HMG-CoA reductase inhibitors, adverse reactions are usually mild, transient and comparable to placebo.

Product Monograph available on request.

*Registered trademark of Sandoz Canada Inc.

LES-95-08-3232E

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GIVEN THE LATEST CLINICAL EVIDENCE...

Why Complicate Osteoarthritis Pain Relief?

A recent study suggests that the pain of osteoarthritis can be effectively managed with a simple analgesic instead of NSAIDs[1].

That's because osteoarthritis pain is often mechanical and noninflammatory. It results from structural changes in and around weight-bearing joints[2]. These changes may cause pain on motion even in the absence of active inflammation[3].

You can control regular osteoarthritis pain by using Extra Strength TYLENOL* acetaminophen, while reserving ASA and other NSAIDs for periodic acute flares.

Extra Strength TYLENOL* delivers effective pain relief. And side effects are rare[4]. Specifically, Extra Strength TYLENOL* is unlikely to complicate therapy with gastrointestinal upset or by interacting with commonly prescribed drugs, including antihypertensives and diuretics.

Recommend 1000 mg (two caplets) of Extra Strength TYLENOL* q.i.d. p.r.n. for proven relief of mechanical osteoarthritis pain coupled with an excellent safety profile.

Unsurpassed Efficacy and Safety Combination[4]

SPECIFY TWO EXTRA STRENGTH TYLENOL* acetaminophe

Easy To Open package commended by THE ARTHRITIS SOCIETY

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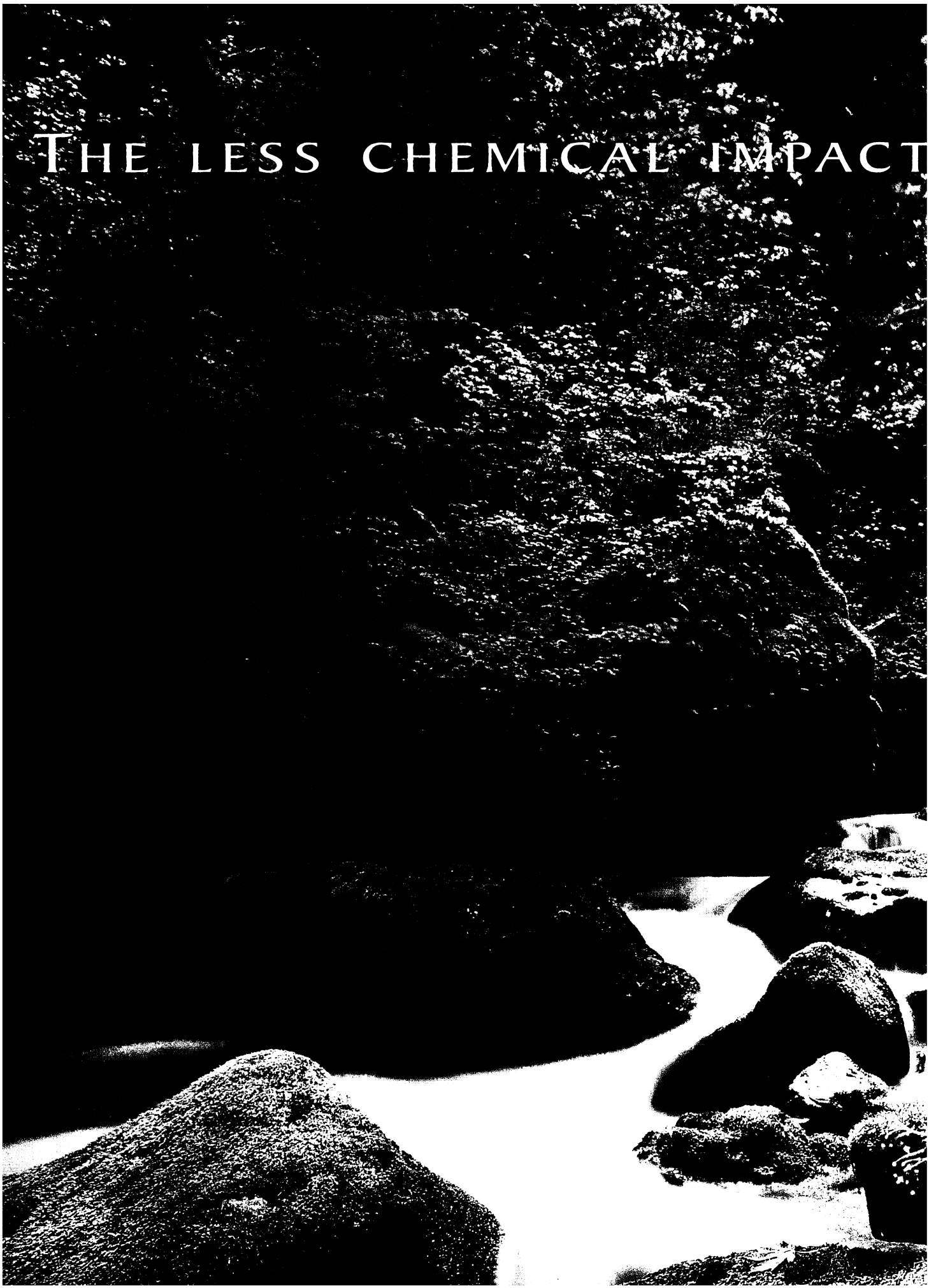
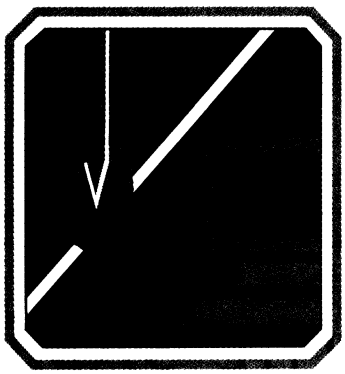
Participation by The Arthritis Society in this promotion does not imply product endorsement.


THE LESS CHEMICAL IMPACT

For prescribing information see page 600

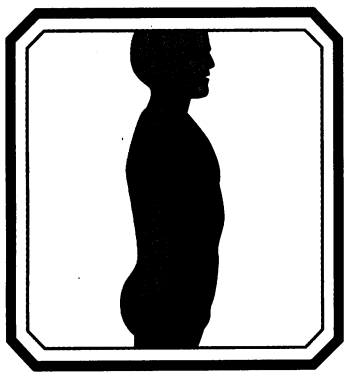
COLUMBIA REHABILITATION CENTRES

F.A.E.

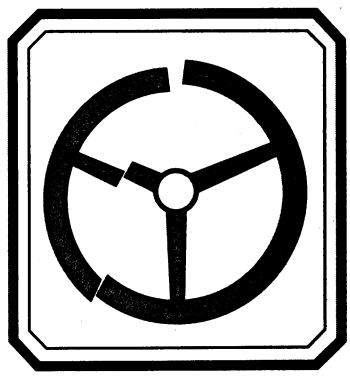


Sports Injuries

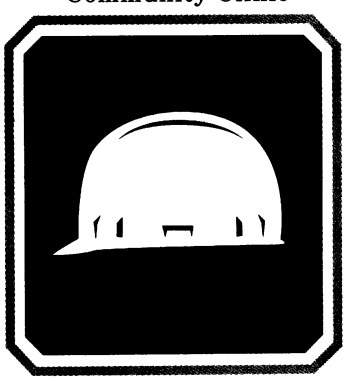
Orthopaedic



MVA Program

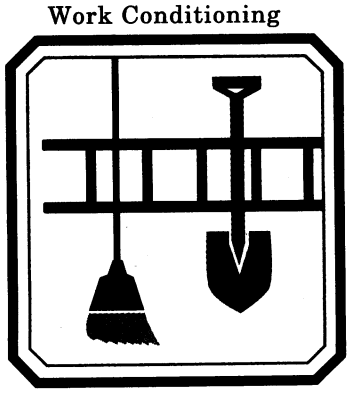


Community Clinic

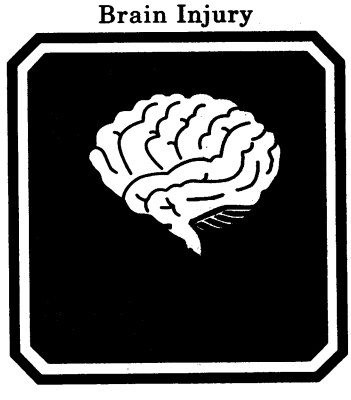


Pain Management

Work Conditioning



Brain Injury



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FIRST-LINE... FOR SUCCESSFUL OUTCOMES

INTRODUCING A NEW FIRST-LINE ANTIDEPRESSANT TO SUCCESSFULLY TREAT A BROAD RANGE OF DEPRESSED PATIENTS

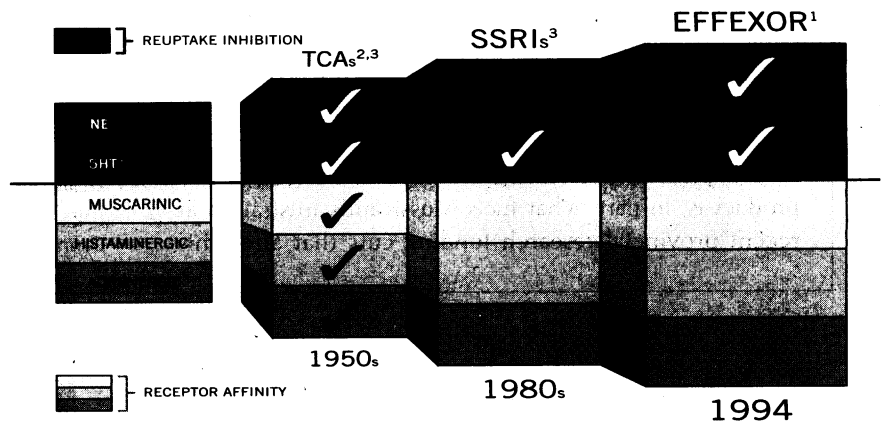
A NEW TARGETED DUAL ACTION SEROTONIN AND NOREPINEPHRINE REUPTAKE INHIBITOR

For treating a broad range of depressed patients

EFFEXOR is a unique compound that is chemically different from current antidepressants.[1] EFFEXOR has no significant affinity for the receptors generally held responsible for causing dry mouth, dizziness, sedation, cardiac problems and other nuisance side-effects associated with other antidepressants.[1-3]

Pharmacologic activity:
√ = strong affinity
NE = norepinephrine
5HT= serotonin
TCA = tricyclic
SSRI= selective serotonin reuptake inhibitor

*Serotonin reuptake inhibition varies among TCAs. The clinical significance of these *in vitro* data is unknown.



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Montreal, Canada
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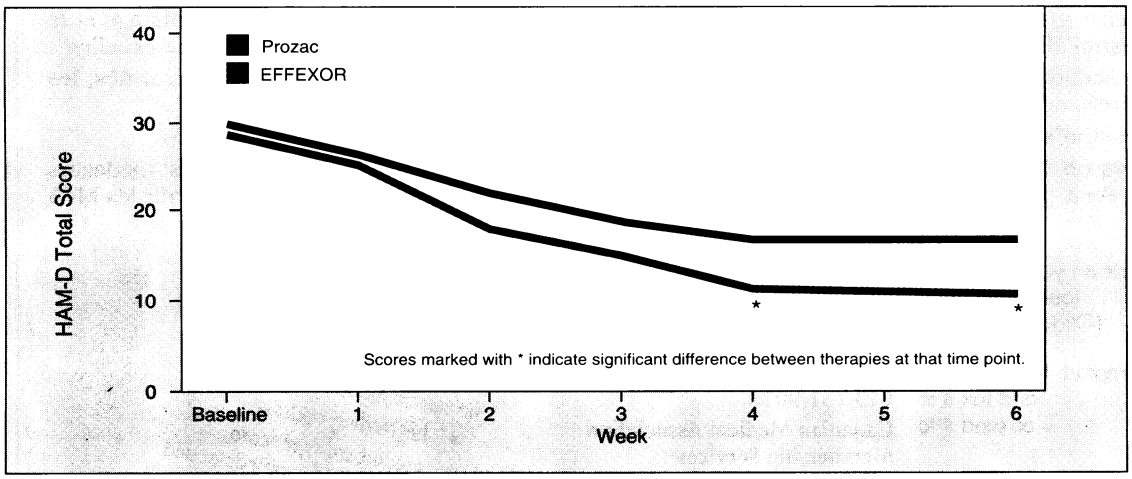
SEROTONIN
NOREPINEPHRINE
REUPTAKE
INHIBITOR

MORE EFFECTIVE THAN PROZAC

in a comparative study of severely depressed patients

EFFEXOR can be considered a first-line therapy in the treatment of major depression because of its effectiveness, low toxicity in overdose, and mild side-effect profile.[5†]

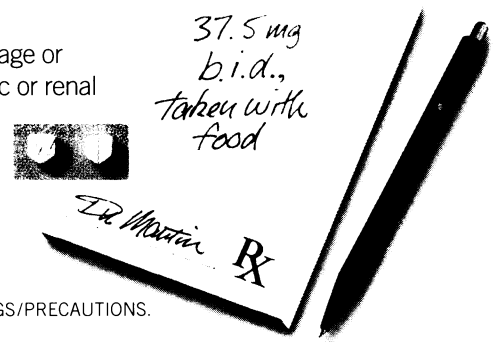
Improvement in total scores on HAM-D rating scale



(Adapted from Clerc G.E., *et al*[4]) 6-week, randomized, double-blind comparative study of EFFEXOR (venlafaxine) and "Prozac" (fluoxetine HCl) in hospitalized patients with major depression and melancholia. Maximum and study dosage: EFFEXOR 200 mg/day Prozac 40 mg/day Effexor n=33 Prozac n=34. All on-therapy values for HAM-D are significantly different ($p \leq 0.05$) from baseline values.

75 MG/DAY IS THE RECOMMENDED DOSAGE FOR MOST PATIENTS*

*In 2 or 3 divided doses, taken with food. No dose adjustments necessary due to age or gender alone, however, dosage reduction is recommended in patients with hepatic or renal impairment.[1] See Prescribing Information for detailed dosage recommendations.



EFFEXOR MEDICAL INFORMATION LINE:1-800-461-8844
(For physicians and pharmacists)

† Some of the most commonly observed events (incidence > 5% and twice that of placebo) were asthenia, nausea, anorexia, somnolence, dry mouth and sexual dysfunction in men.[1]

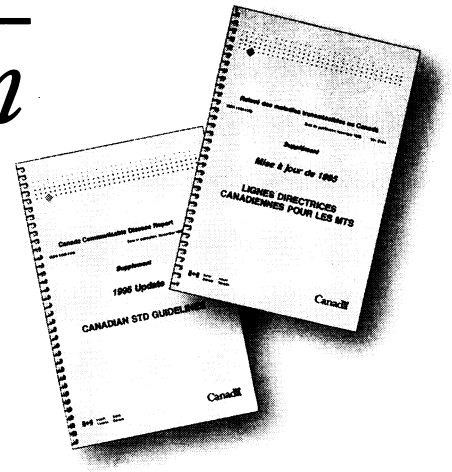
BEFORE PRESCRIBING, PLEASE SEE WARNINGS/PRECAUTIONS.

Pr EFFEXOR®

VENLAFAXINE HCl TABLETS

For prescribing information see page 590

Selection ☑ Sélection



Canadian STD Guidelines — 1995 Update

The revised edition of the clinician's guide to sexually transmitted diseases in Canada

- important new information in nine chapters
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- detailed explanation of diagnosis, management and treatment procedures
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- extensive tables and appendices
- strong emphasis on the role physicians can play in helping their patients prevent STDs

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La version révisée du guide du clinicien pour les maladies transmises sexuellement au Canada

- nouveaux renseignements importants présentés en neuf chapitres
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Please send me _____ copies of ***Canadian STD Guidelines*** today.
Veuillez me faire parvenir _____ exemplaires des ***Lignes directrices canadiennes pour les MTS***

❒ Cheque or money order *(payable to the Canadian Medical Association)*
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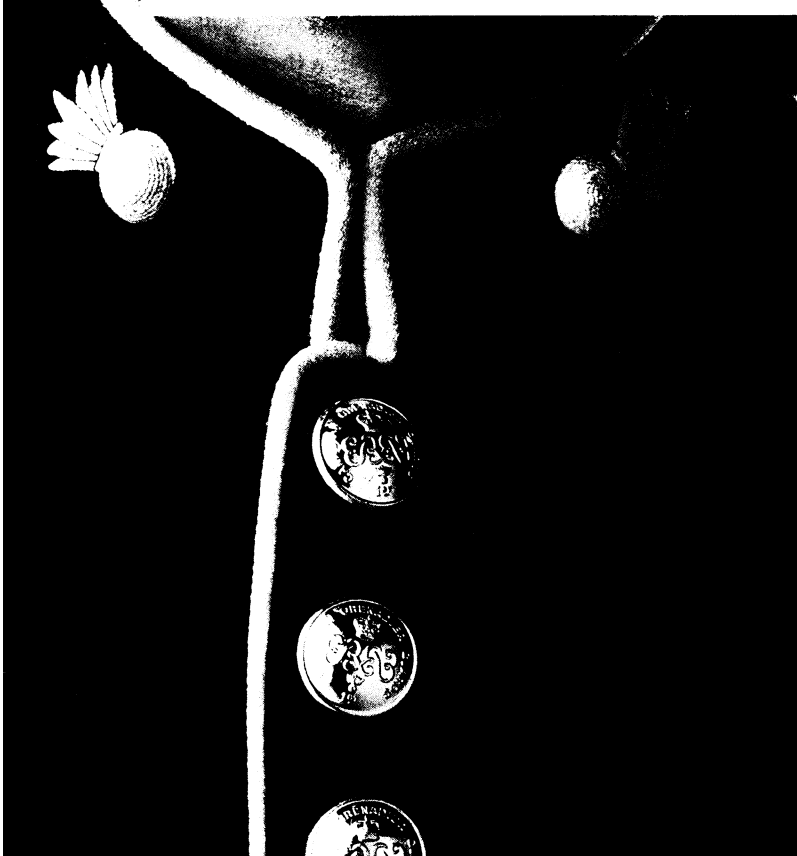
Subtotal **Total partiel**		_____
7% GST/TPS		_____
Total		_____

GST registration #/N° d'enregistrement TPS 121 765 705

on guard

low cough <1.0%

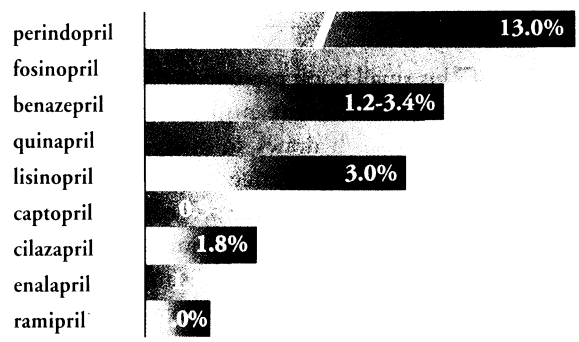


ALTACE®
ramipril

BODYGUARD FOR HYPERTENSIVES

- **Overall reported incidence of cough is <1%[5†]**
- **Discontinuation rate of only 0.8%[5]**
- **Helps ensure patient compliance**

Comparative rate of cough[7*]

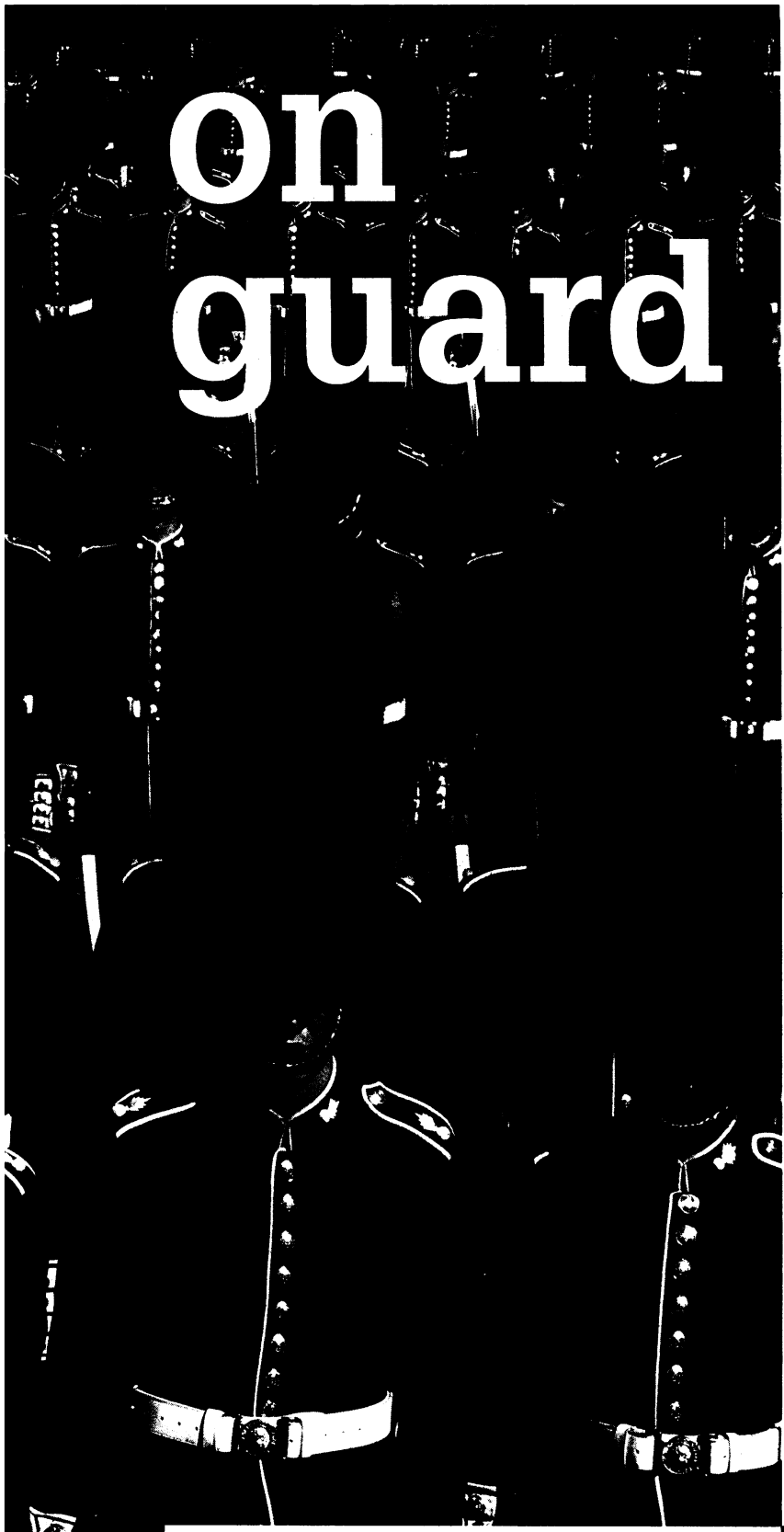


*Data compiled from product monographs which are based on different data bases. As a result, adverse events/discontinuations may not be predictive of comparative rates in clinical practice. The most frequent adverse events occurring in clinical trials with Altace were headache and dizziness.

In one study, increased cough was seen in almost 12% of patients.

PMAC AD ALT-03-95

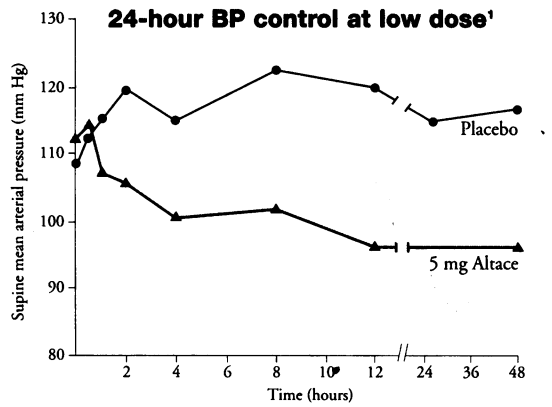
Hoechst-Roussel Canada Inc.



ALTACE® ramipril

BODYGUARD FOR HYPERTENSIVES

- **Smooth, effective blood pressure control for a full 24 hours[1]**
- **Control is commensurate with normal diurnal fluctuations[1]**
- **Can provide effective blood pressure control – even during the last stages of the dosing period.[1,2]**



Adapted from Todd PA and Benfield P.

"The maximum antihypertensive response [with Altace] occurred about 4 hours after administration and blood pressure was still significantly reduced after 24... hours."[1]

smooth 24 hours *plus*

Altace is indicated in the treatment of essential hypertension, normally when ß-blockers or diuretics are inappropriate.

MEMBER PMAC PAAB AD-ALT-02-95 **Hoechst-Roussel Canada Inc.**

BOOKS FOR PATIENTS

Coping with Chronic Fatigue Syndrome: Nine Things You Can Do. Fred Friedberg. 166 pp. New Harbinger Publications, Inc./Raincoast Book Distribution Limited, Vancouver. 1995. $37.50, hardcover; $19.50, paperback. ISBN 1-57224-020-2, hardcover; ISBN 1-57224-019-9, paperback

Deaf Young People and their Families: Developing Understanding. Susan Gregory, Juliet Bishop and Lesley Sheldon. 361 pp. Cambridge University Press, New York. 1995. Price not stated. ISBN 0-52142998-6

Every Pregnant Woman's Guide to Preventing Premature Birth: a Program for Reducing the Sixty Proven Risks That Can Lead to Prematurity. Barbara Luke. 239 pp. Illust. Random House of Canada, Ltd., Mississauga. 1995. $32. ISBN 0-8129-2472-X

ETHICS

Ethics in Emergency Medicine. 2nd ed. Kenneth V. Iserson, Arthur B. Sanders, Deborah Mathieu. 519 pp. Galen Press, Ltd., P.O. Box 64400, Tucson AZ 85728-4400. 1995. $39.95 (US). ISBN 1-883620-14-7

HISTORY

Aboriginal Health in Canada: Historical, Cultural, and Epidemiological Perspectives. James B. Waldram, D. Ann Herring and T. Kue Young. 334 pp. Illust. University of Toronto Press, Toronto. 1995. $18.95 (US). ISBN 0-8020-6887-1

Bamboo Stone: the Evolution of a Chinese Medical Elite. Karen Minden. 201 pp. Illust. University of Toronto Press, Toronto. 1994. Price not stated. ISBN 0-8020-0550-0

Souvenirs: Université d'Ottawa, Faculté de médecine, 1945–1995; Memories: University of Ottawa, Faculty of Medicine 1945–1995. Edited by Roger Broughton, Toby Gelfand, Gilles Hurteau, John Last, George Taylor and James J. Wiley. 231 pp. Illust. University of Ottawa, Ottawa. 1995. $25. ISBN 0-88927-044-9

HIV/AIDS

Seeking Fair Treatment: From the AIDS Epidemic to National Health Care Reform. Norman Daniels. 204 pp. Oxford University Press, Oxford, England; Oxford University Press Canada, Don Mills, Ont. 1995. $37. ISBN 0-19-505712-0

MISCELLANEOUS

Diabetes in America. 2nd ed. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. 782 pp. Illust. National Diabetes Information Clearinghouse, National Institute of Diabetes and Digestive and Kidney Diseases, 1 Information Way, Bethesda MD 20892-3560. 1995. $20 (US). Price includes shipping and handling.

Diving and Subaquatic Medicine. 3rd ed. Carl Edmonds, Christopher Lowry and John Pennefather. 565 pp. Butterworth-Heinemann Ltd., Oxford, England; Butterworth-Heinemann, Boston. 1994. $55 (US). ISBN 0-7506-2131-1

Fibromyalgia, Chronic Fatigue Syndrome, and Repetitive Strain Injury: Current Concepts in Diagnosis, Management, Disability, and Health Economics. Edited by Andrew Chalmers, Geoffrey Owen Littlejohn, Irving E. Salit and Frederick Wolfe. 182 pp. Haworth Medical Press, Haworth Press, Inc., New York. 1995. $24.95 (US). ISBN 1-56024-744-4

NEUROLOGY

Ethical Issues in Neurology. James L. Bernat. 364 pp. Butterworth-Heinemann Ltd., Oxford, England; Butterworth-Heinemann, Boston. 1994. $55 (US). ISBN 0-7506-9501-3

Metabolic Myopathies. David Hilton-Jones, Marian V. Squier, Doris Taylor and Paul M. Matthews. *Major Problems in Neurology Series* no. 29. 281 pp. Illust. W.B. Saunders Company/Harcourt Brace & Company, Philadelphia; W.B. Saunders Canada, Toronto. 1995. $97. ISBN 0-7020-1607-1

Movement Disorders 1 and 2 Reissue. Edited by C. David Marsden and Stanley Fahn. *Blue Books of Practical Neurology Series*, nos. 2 and 7. 468 pp. Illust. Butterworth-Heinemann Ltd., Oxford, England; Butterworth-Heinemann, Boston. 1995. $135 (US). ISBN 0-7506-2232-6.

ONCOLOGY

Autobiography of a Face. Lucy Grealy. 223 pp. HarperCollins Publishers, Inc., New York; HarperCollins Canada Ltd., Toronto. 1994. $16.75. ISBN 0-06-097673-X

PEDIATRICS

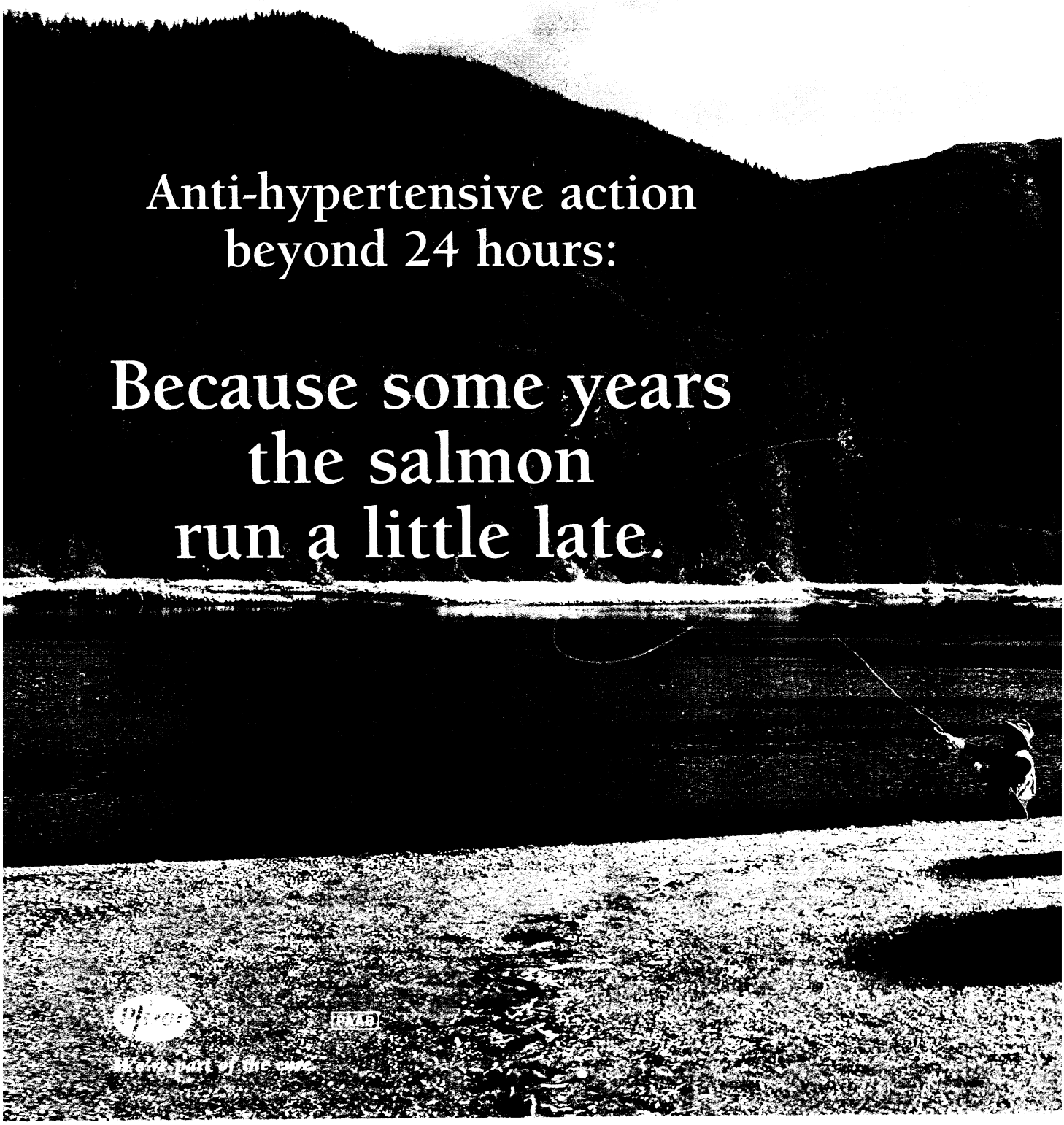
Glue Ear in Childhood: a Prospective Study of Otitis Media with Effusion. A. Richard Maw. *Clinics in Developmental Medicine*, no. 135. 136 pp. Illust. Cambridge University Press, New York. 1995. $49.95 (US). ISBN 0-898683-03-4

PHARMACOLOGY

Compendium of Nonprescription Products. 2nd ed. Edited by M. Claire Gillis. 599 pp. Canadian Pharmaceutical Association, Ottawa. 1995. Price not stated. ISBN 0-919115-70-5

PSYCHIATRY

Satanic Ritual Abuse: Principles of Treatment. Colin A. Ross. 228 pp. University of Toronto Press, Toronto. 1995. $16.95. ISBN 0-8020-7357-3



And in this morning's rush to get away from it all, he forgot his therapy at home.

He just became one of the 62% of Canadian hypertensives who regularly miss, forget or delay taking their medication (n=301).

Of course, patients should be advised to take Norvasc® every 24 hours. But even a full 24 hours after a missed dose, long-acting Norvasc® maintains blood levels which can deliver blood pressure reduction.

With proven tolerability and, at 1.9%, an extremely low discontinuation rate.

Once-a-day Norvasc®. Because the best things in life usually arrive in their own good time.

Norvasc® is indicated in the treatment of mild to moderate essential hypertension where diuretics or beta-blockers are unsuitable. The most common adverse reactions include edema 8.0% and headache 8.3%.

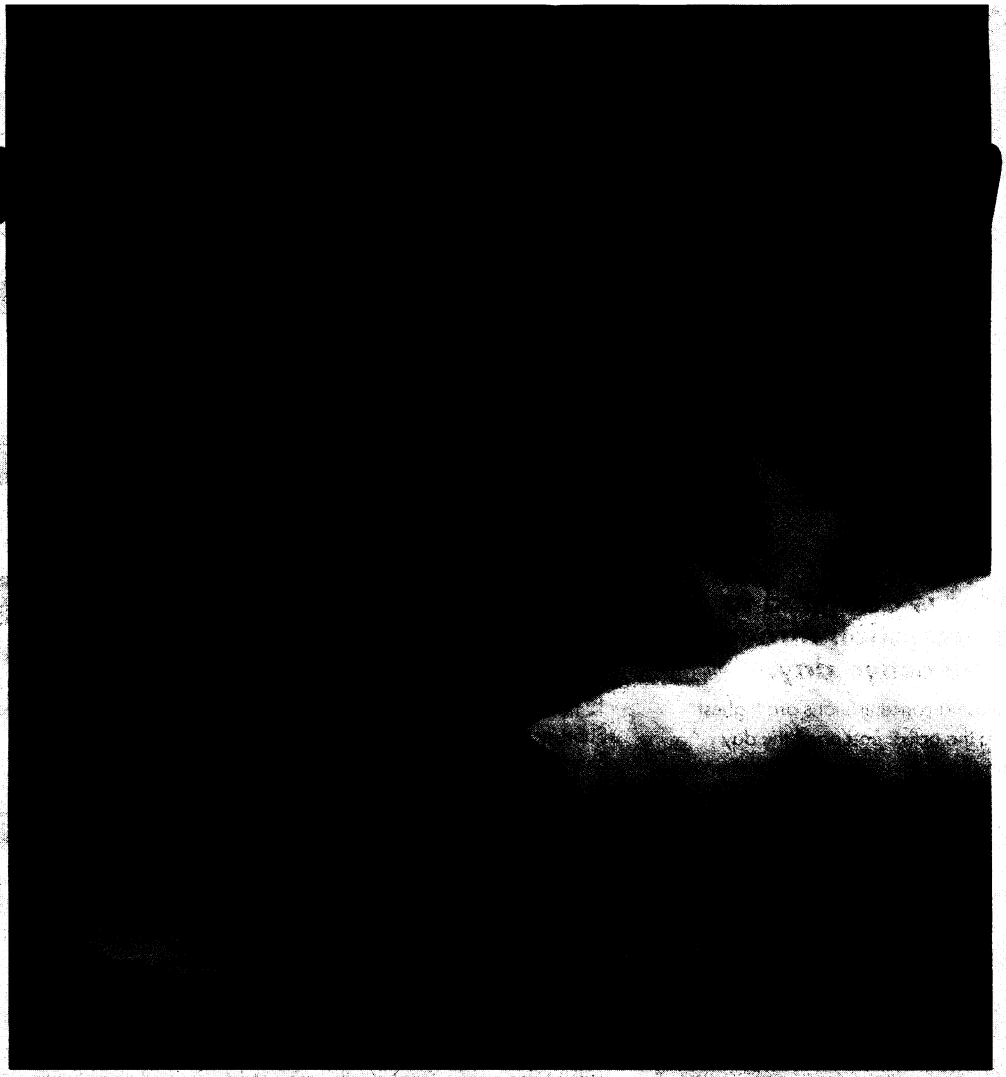
Pr NORVASC*

(amlodipine besylate/pfizer)

Allows extra time for human nature.

For prescribing information see page 601

Po ce



In a recent study involving 4,444 patients[1]:

- *Multicentre, double-blind, placebo-controlled*
- *Patients with angina or post-MI*
- *5.4 years mean follow-up*

Proven highly effective

- *38% mean reduction in LDL-C by 6 weeks*

Proven long-term tolerability

Discontinuation due to adverse effects similar in the ZOCOR® (5.7%) and placebo (5.8%) groups

Pr ZOCOR®

(simvastatin tablets)

Evidence-based therapy

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DIV. OF MERCK FROSST CANADA INC.
KIRKLAND, QUEBEC

BEFORE PRESCRIBING PLEASE CONSULT PRESCRIBING INFORMATION

ZOCOR® is indicated as an adjunct to diet for the reduction of elevated total and LDL-cholesterol levels in patients with primary hypercholesterolemia, when diet and other non-pharmacologic measures alone have been inadequate.

PAAB

ZCR-95-CDN-8526-JA

Imdur® ONCE-A-DAY
EXTENDED RELEASE ISOSORBIDE-5-MONONITRATE

IMDUR ONCE-A-DAY HELPS KEEP ANGINA AND TOLERANCE AWAY.

INDICATION

Prevention of anginal attacks in chronic stable angina pectoris associated with coronary artery disease.[1]

KEY PATIENT BENEFITS

Once-a-day oral form can improve compliance. Isosorbide-5-mononitrate (5-ISMN) is released over a 10 hour period providing effective protection against angina for up to 12 hours.[1] Designed to avoid tolerance and maintain efficacy throughout long-term use.[1,2]
Short-acting nitroglycerin requirements are usually reduced.[2]
Exercise capacity is usually increased.[1]

COMPARED TO OTHER NITRATES

Oral Nitrates: 5-ISMN is the active metabolite of isosorbide dinitrate (ISDN) with a half-life of 5 hours.[1] It is almost totally bioavailable because it is not subject to first pass metabolism in the liver.[1] Imdur offers highly predictable and reliable therapeutic effects for up to 12 hours.[1]
Plasma concentrations fall gradually in the second half of the dosage interval.[1]
Hemodynamic responses to 5-ISMN are similar to those of other nitrates.[1]

Transdermal Patches: Imdur is a once-a-day oral form designed to simplify patient dosing.[1] Optimal results with patches depend on patient's adherence to a twice-daily (patch-on and patch-off) routine.[3]

ADVERSE REACTIONS

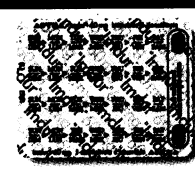
The most common adverse effects are headache, dizziness, fatigue, nausea and flushing.[1] Headache is most prominent during the first 4 days and its incidence is reduced when 30 mg (½ tablet) is used as the starting dose.[1,4]

DOSING

One 60 mg tablet of Imdur is recommended once-a-day on arising.
The dose may be increased to two tablets once daily. To minimize the chance of headache, treatment can be initiated with 30 mg (½ tablet) for the first 2-4 days.[1]

AVAILABILITY

Imdur is provided in a convenient 30 day compliance package to help simplify and improve patient adherence to therapy.

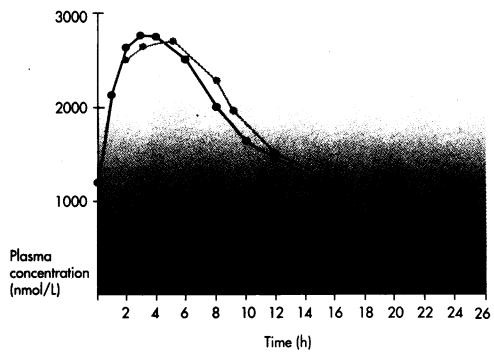


DRUG COST

The daily drug cost for patients continuing to receive Imdur (60 mg) is $0.64 plus dispensing fee. This is lower than the daily drug cost of standard dosages of any other controlled or extended release form of nitrate, oral or transdermal, listed on drug formulary.[5]

Imdur is designed to provide protection throughout the active day.

Imdur plasma concentrations are highest during the active portion of the day when administered on arising as recommended.



5-ISMN steady-state plasma concentrations after oral administration of Imdur once daily (mean ± SE) in 8 healthy subjects (•) and 6 angina patients (•).[6]

Imdur® ONCE-A-DAY
EXTENDED RELEASE ISOSORBIDE-5-MONONITRATE

60 mg 30 mg 30 mg

Actual size

Imdur is the only once-a-day nitrate which can be halved allowing one prescription to initiate and continue therapy.

ASTRA

Astra Pharma Inc., Mississauga, Ontario L4Y 1M4

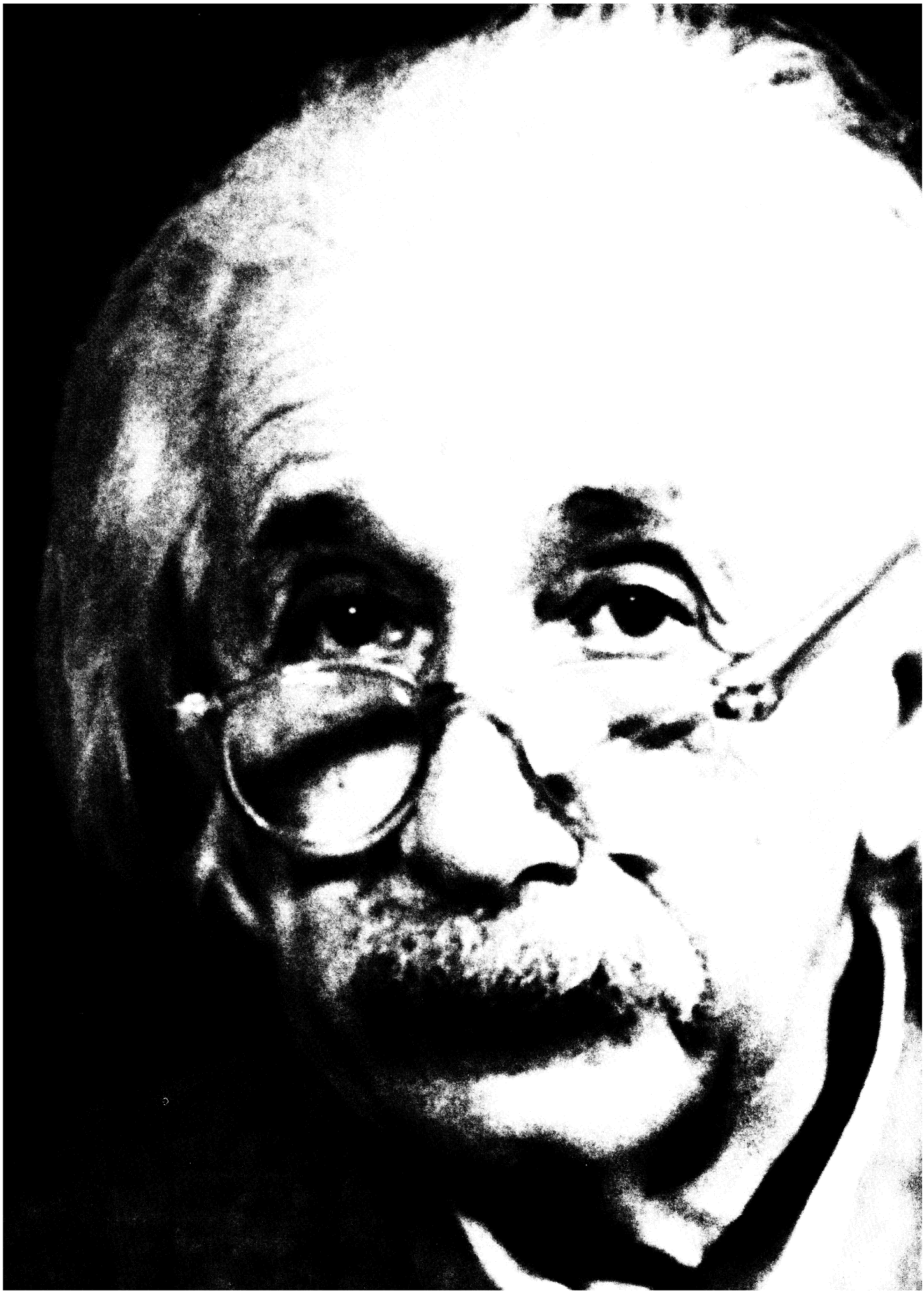
Bayer

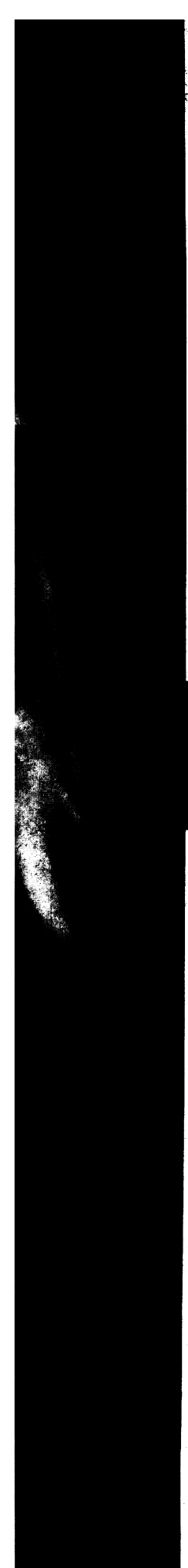
Healthcare Division

PAAB

Adalat XL (nifedipine extended release tablets) is an antihypertensive/antianginal agent. Full prescribing information is available upon request.
Bayer Inc. 77 Belfield Road, Etobicoke, Ontario M9W 1G6.

XL 432–1195E





Now on Québec and Ontario Formularies.

That's why, with its powerful activity against

H. influenzae,[1,2] Biaxin* is a smart choice.

It has proven clinical success in acute

exacerbations of chronic bronchitis.[3,4]

H. influenzae has a touch of genius too.

And tolerability† comparable to cephalosporins.[4,5]

Even the brainiest pathogen can be outwitted

with Biaxin.

For today's bronchitis.

Pr BIAXIN® 250

CLARITHROMYCIN *mg tablets*

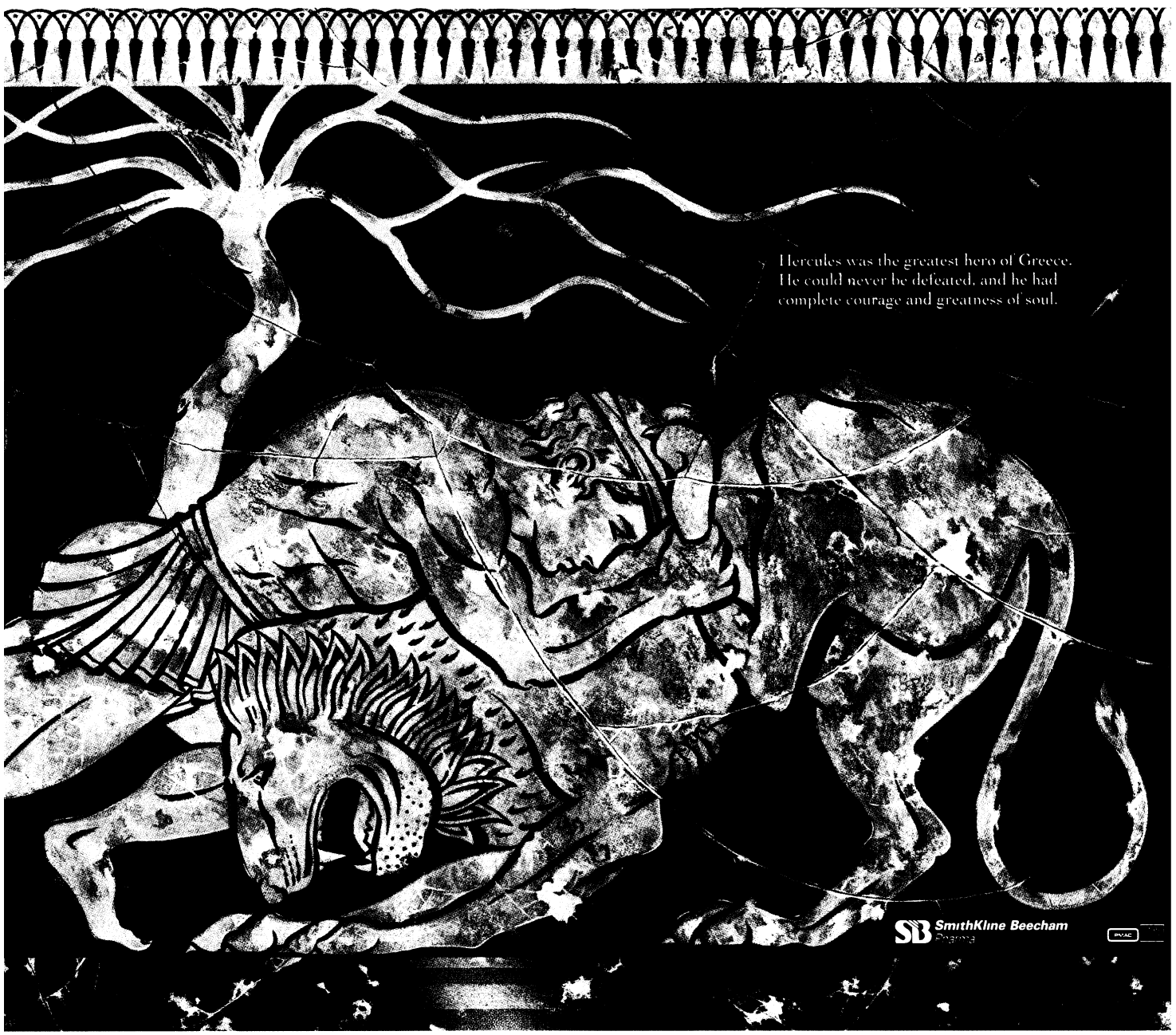
Albert Einstein licensed by The Roger Richman Agency, Inc., Beverly Hills, CA.

*Biaxin is indicated for Acute Exacerbation of Chronic Bronchitis (AECB) caused by *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*.

†Adverse reactions were mild and transient. The most frequent were nausea (4%) and diarrhea (3%).

COMMITTED TO THE CONQUEST OF INFECTIOUS DISEASE

For prescribing information see page 588



OVERCOMING SYMPTOMS OF ANXIETY CAN GIVE YOUR PATIENTS THE COURAGE TO VANQUISH DEPRESSION

If anxiety symptoms associated with depression aren't controlled early, patients may terminate therapy[1]

Paxil has been proven as effective as fluoxetine and TCAs at relieving depression – but with Paxil, symptoms of anxiety may begin to subside as early as the second week of treatment.[2-6]

Paxil is also well tolerated by most patients, with the most common adverse effects being those associated with the SSRI class (including nausea, somnolence and asthenia).

Once a day
Paxil®
paroxetine HCl

Ending the dark night of depression and its anxiety

THE ONLY SSRI INDICATED FOR PANIC DISORDER AND OCD

THE ONLY SSRI INDICATED FOR PANIC DISORDER

Paxil has been proven effective in the treatment of panic disorder. Furthermore, the side effects most commonly seen are those associated with the SSRI class (including somnolence and asthenia). And there have been no reports of dependence in patients receiving Paxil.

Paxil, to still the rustling of panic.

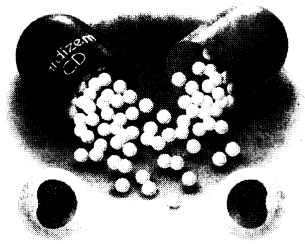
Once a day
Paxil®
paroxetine HCl

Ending the dark night of depression and its anxiety

SB SmithKline Beecham Pharma

PMAC PAAB CCPP

Therapeutic Index



Once-a-day

®CARDIZEM® CD

Controlled Delivery diltiazem HCl/MMDC

PRESCRIBING INFORMATION

CARDIZEM CD Once-a-day Controlled Delivery Capsules 120 mg, 180 mg, 240 mg and 300 mg.

THERAPEUTIC CLASSIFICATION

Antihypertensive and Antianginal agent.

INDICATIONS AND CLINICAL USE

Angina

1. CARDIZEM CD is indicated for the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta-blockers and/or organic nitrates or who cannot tolerate those agents.
2. CARDIZEM CD may be tried in combination with beta-blockers in chronic stable angina patients with normal ventricular function. When such concomitant therapy is introduced, patients must be monitored closely (See WARNINGS).
3. Since the safety and efficacy of CD capsules in the management of unstable or vasospastic angina has not been substantiated, use of this formulation for these indications is not recommended.

Hypertension

CARDIZEM CD is indicated for the treatment of mild to moderate essential hypertension. CARDIZEM CD should normally be used in those patients in whom treatment with diuretics or beta-blockers has been ineffective, or has been associated with unacceptable adverse effects.
CARDIZEM CD can be tried as an initial agent in those patients in whom the use of diuretics and/or beta-blockers is contraindicated, or in patients with medical conditions in which these drugs frequently cause serious adverse effects.
Safety of concurrent use of CARDIZEM CD with other antihypertensive agents has not been established.

CONTRAINDICATIONS

Diltiazem HCl is contraindicated:

1. In patients with sick sinus syndrome except in the presence of a functioning ventricular pacemaker;
2. In patients with second or third degree AV block;
3. In patients with known hypersensitivity to diltiazem;
4. In patients with severe hypotension (less than 90 mm Hg systolic);
5. In myocardial infarction patients, who have left ventricular failure manifested by pulmonary congestion;
6. In pregnancy and in women of child-bearing potential.

WARNINGS

Cardiac Conduction

Diltiazem prolongs AV node refractory periods without significantly prolonging sinus node recovery time, except in patients with sick sinus syndrome. This effect may rarely result in abnormally slow heart rates (particularly in patients with sick sinus syndrome) or second- or third-degree AV block (6 of 1208 patients or 0.5%).
First degree AV block was observed in 5.8% of patients receiving CARDIZEM CD (see ADVERSE REACTIONS).
Concomitant use of diltiazem with beta-blockers or digitalis may result in additive effects on cardiac conduction.

Congestive Heart Failure

Because diltiazem has a negative inotropic effect *in vitro* and it affects cardiac conduction, the drug should only be used with caution and under careful medical supervision in patients with congestive cardiac failure (see also CONTRAINDICATIONS).

Use with Beta-blockers

The combination of diltiazem and beta-blockers warrants caution since in some patients additive effects on heart rate, AV conduction, blood pressure or left ventricular function have been observed. Close medical supervision is recommended.
Generally, diltiazem should not be given to patients with impaired left ventricular function while they receive beta-blockers. However, in exceptional cases when, in the opinion of the physician, concomitant use is considered essential, such use should be instituted gradually in a hospital setting.
Diltiazem gives no protection against the dangers of abrupt beta-blocker withdrawal and such withdrawal should be done by the gradual reduction of the dose of beta-blocker.

Hypotension

Since diltiazem lowers peripheral vascular resistance, decreases in blood pressure may occasionally result in symptomatic hypotension. In patients with angina or arrhythmias using antihypertensive drugs, the additional hypotensive effect of diltiazem should be taken into consideration.

Acute Hepatic Injury

In rare instances, significant elevations in alkaline phosphatase, CPK, LDH, SGOT, SGPT and symptoms consistent with acute hepatic injury have been observed. These reactions have been reversible upon discontinuation of drug therapy. Although a causal relationship to diltiazem has not been established in all cases, a drug induced hypersensitivity reaction is suspected (see ADVERSE REACTIONS). As with any drug given over prolonged periods, laboratory parameters should be monitored at regular intervals.

PRECAUTIONS

Impaired Hepatic or Renal Function

Because diltiazem is extensively metabolized by the liver and excreted by the kidney and in bile, monitoring of laboratory parameters and cautious dosage titration are recommended in patients with impaired hepatic or renal function (see ADVERSE REACTIONS).

Pediatric Use

The safety of diltiazem in children has not yet been established.

Nursing Mothers

Diltiazem has been reported to be excreted in human milk. One report suggests that concentrations in breast milk may approximate serum levels. Since diltiazem safety in newborns has not been established, it should not be given to nursing mothers.

Use in the Elderly

Administration of diltiazem to elderly patients (over or equal to 65 years of age) requires caution. The incidence of adverse reactions is approximately 13% higher in this group. Those adverse reactions which occur more frequently include: peripheral edema, bradycardia, palpitation, dizziness, rash and polyuria. Therefore, particular care in titration is advisable (see DOSAGE AND ADMINISTRATION).

Drug Interactions

Digitalis: Diltiazem and digitalis glycosides may have an additive effect in prolonging AV conduction. In clinical trials, concurrent administration of diltiazem and digoxin have resulted in increases in serum digoxin levels with prolongation of AV conduction. This increase may result from a decrease in renal clearance of digoxin. Patients on concomitant therapy, especially those with renal impairment, should be carefully monitored. The dose of digoxin may need downward adjustment.
Beta-blockers: The concomitant administration of diltiazem with beta adrenergic blocking drugs warrants caution and careful monitoring. Such an association may have an additive effect on heart rate, on AV conduction or on blood pressure. (See WARNINGS.) Appropriate dosage adjustments may be necessary. A study in five normal subjects showed that diltiazem increased propranolol bioavailability by approximately 50%.
Short and Long-acting Nitrates: Diltiazem may be safely co-administered with nitrates, but there have been few controlled studies to evaluate the antianginal effectiveness of this combination.
Other Calcium Antagonists: Limited clinical experience suggests that in certain severe conditions not responding adequately to verapamil or to nifedipine, using diltiazem in conjunction with either of these drugs may be beneficial.

ADVERSE REACTIONS

Angina

The safety of CARDIZEM CD, administered at doses up to 360 mg a day, was evaluated in 365 patients with chronic stable angina treated in controlled and open-label clinical trials. Adverse events were reported in 21.1% of patients, and required discontinuation in 2.2% of patients. The most common adverse effects reported were: first degree AV block (5.8%), dizziness (3.0%), headache (3.0%), asthenia (2.7%). bradycardia (2.5%), and angina pectoris (1.6%). The following percentage of adverse effects, divided by system, was reported:
Cardiovascular: First degree AV block (5.8%), bradycardia (2.5%), angina pectoris (1.6%), peripheral edema (1.4%), palpitations (1.1%), and ventricular extrasystoles (0.8%).
Central Nervous System: Dizziness (3.0%), headache (3.0%), asthenia (2.7%), insomnia (1.1%), nervousness (0.8%).
Gastrointestinal: Nausea (1.4%), diarrhea (0.5%).
Dermatological: Rash (0.8%).
Other: Amblyopia (0.5%).
The following additional adverse effects have occurred with an incidence of less than 0.5% in clinical trials: bundle branch block, ventricular tachycardia, ECG abnormality, supraventricular extrasystoles, chest pain, syncope, postural hypotension, paresthesia, tremor, depression, mental confusion, impotence, abdominal pain, constipation, GI disorder, epistaxis, nuchal rigidity, myalgia.

Hypertension

A safety evaluation was carried out in controlled studies in 378 hypertensive patients treated with CARDIZEM CD at doses up to 360 mg a day. Adverse effects were reported in 30.7% of patients and required discontinuation of therapy in 2.1%. The most common adverse effects were: headache (8.7%); edema (4.0%); bradycardia (3.7%); dizziness (3.4%), ECG abnormality (2.9%); asthenia (2.6%) and first degree AV block (2.1%).
The following percentage of adverse effects, divided by system, was reported:
Cardiovascular: Edema peripheral (4.0%), bradycardia (3.7%), ECG abnormalities (2.9%), first degree AV block (2.1%), arrhythmia (1.6%), vasodilation (flushing) (1.6%), bundle branch block (0.8%), cardiomegaly (0.5%), hypotension (0.5%).
Central Nervous System: Headache (8.7%), dizziness (3.4%), asthenia (2.6%), somnolence (1.3%), nervousness (1.1%).
Gastrointestinal: Constipation (1.3%), dyspepsia (1.3%), diarrhea (0.6%).
Laboratory Tests: SGPT increase (0.8%).
Other: Leukopenia (1.1%), nocturia (0.5%).
The following additional adverse effects have occurred with an incidence of less than 0.5% in clinical trials: systolic murmur, supraventricular extrasystoles, migraine, tachycardia, increased appetite, increase in weight, albuminuria, bilirubinemia, hyperuricemia, thirst, insomnia, vertigo, nausea, pruritus, rash, increased perspiration, polyuria, amblyopia, tinnitus, and elevations in creatine kinase, alkaline phosphatase, and SGOT.

OVERALL CARDIZEM SAFETY PROFILE

In clinical trials of CARDIZEM tablets, CARDIZEM SR capsules and CARDIZEM CD capsules involving over 3300 patients, the most common adverse reactions were headache (4.6%), edema (4.6%), dizziness (3.5%), asthenia (2.7%), first-degree AV block (2.4%), bradycardia (1.7%), flushing (1.5%), nausea (1.4%), rash (1.2%), and dyspepsia (1.0%). In addition, the following events were reported with a frequency of less than 1.0%.
Cardiovascular: Angina, arrhythmia, bundle branch block, tachycardia, ventricular extrasystoles, congestive heart failure, syncope, palpitations, AV block (second- or third-degree), hypotension, ECG abnormalities.
Nervous System: Amnesia, depression, gait abnormality, nervousness, somnolence, hallucinations, paresthesia, personality change, tinnitus, tremor, abnormal dreams, insomnia.
Gastrointestinal: Anorexia, diarrhea, dysgeusia, mild elevations of SGOT, SGPT, LDH, and alkaline phosphatase (see WARNINGS), vomiting, weight increase, thirst, constipation.
Dermatological: Petechiae, pruritus, photosensitivity, urticaria.
Other: Amblyopia, CPK increase, dyspnea, epistaxis, eye irritation, hyperglycemia, sexual difficulties, nasal congestion, nocturia, osteoarticular pain, impotence, dry mouth, polyuria, hyperuricemia.
The following postmarketing events have been reported infrequently in patients receiving CARDIZEM: alopecia, erythema multiforme, exfoliative dermatitis, extrapyramidal symptoms, gingival hyperplasia, hemolytic anemia, detached retina, increased bleeding time, leukopenia, purpura, retinopathy, and thrombocytopenia. In addition, events such as myocardial infarction have been observed which are not readily distinguishable from the natural history of the disease in these patients. A number of well-documented cases of generalized rash, characterized as leukocytoclastic vasculitis, have been reported. However, a definitive cause and effect relationship between these events and CARDIZEM therapy is yet to be established.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Overdosage with oral diltiazem has been observed in 9 cases. Eight (8) patients recovered without sequelae over a few days. One patient who had ingested an unknown amount of diltiazem, tolazamide and alcohol experienced a fatal cardiac arrest. Doses ingested ranged from 1.8 to 10.8 grams. Bradycardia, AV block and hypotension were noted in most patients.
In the event of overdosage or exaggerated response, appropriate supportive measures should be employed in addition to gastric lavage. The following measures may be considered:

Bradycardia

Administer atropine. If there is no response to vagal blockade, administer isoproterenol cautiously.

High Degree AV Block

Treat as for bradycardia above. Fixed high degree AV block should be treated with cardiac pacing.

Cardiac Failure

Administer inotropic agents (isoproterenol, dopamine or dobutamine) and diuretics.

Hypotension

Vasopressors (e.g., dopamine or levarterenol bitartrate).
Actual treatment and dosage should depend on the severity of the clinical situation.

DOSAGE AND ADMINISTRATION

Angina

Dosages for the treatment of angina should be adjusted to each patient's needs, starting with a dose of 120 mg to 180 mg once daily. Individual patients may respond to higher doses of up to 360 mg once daily. When necessary, titration should be carried out over a 7 to 14 day period. Patients controlled on diltiazem alone or in combination with other medications may be safely switched to CARDIZEM CD capsules at the nearest equivalent total daily dose. Subsequent titration to higher or lower doses may be necessary and should be initiated as clinically warranted. There is limited experience with doses above 360 mg, however, the incidence of adverse reactions increases as the dose increases with first degree AV block, dizziness, and sinus bradycardia bearing the strongest relationship to dose. Therefore, doses greater than 360 mg are not recommended.

Hypertension

Dosage should be individualized depending on patient's tolerance and responsiveness to CARDIZEM CD capsules. When used as monotherapy, usual starting doses are 180 to 240 mg once daily, although some patients may respond to 120 mg once daily. Maximum antihypertensive effect is usually observed after approximately 2 to 4 weeks of therapy; therefore, dosage adjustments should be scheduled accordingly. The usual dosage range studied in clinical trials was 240 to 360 mg once daily.
A maximum daily dose of 360 mg once daily should not be exceeded.
The dosage of CARDIZEM CD or concomitant antihypertensive agents may need to be adjusted when adding one to the other. See WARNINGS and PRECAUTIONS regarding use with beta-blockers.
Hypertensive patients controlled on CARDIZEM SR alone or in combination with other antihypertensive agents may be safely switched to CARDIZEM CD at the same total daily dose. Subsequent titration to higher or lower doses may be necessary and should be initiated as clinically warranted.
CARDIZEM CD capsules should not be chewed or crushed.

AVAILABILITY

CARDIZEM CD 120 mg capsules are supplied in bottles of 100. Each light turquoise blue capsule is imprinted with CARDIZEM CD 120 mg.
CARDIZEM CD 180 mg capsules are supplied in bottles of 100. Each light blue/light turquoise blue capsule is imprinted with CARDIZEM CD 180 mg.
CARDIZEM CD 240 mg capsules are supplied in bottles of 100. Each light blue/light blue capsule is imprinted with CARDIZEM CD 240 mg.
CARDIZEM CD 300 mg capsules are supplied in bottles of 100. Each light blue/light gray capsule is imprinted with CARDIZEM CD 300 mg.

Product Monograph available on request.

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CANADA
Laval, Quebec H7L 4A8

Paxil®

paroxetine HCl

roxetine (as Paroxetine Hydrochloride)
blets, 20 and 30 mg
erapeutic Classification: Antidepressant - Antiobsessional - Antipanic Agent

DICATIONS AND CLINICAL USE: Depression: Symptomatic relief of depressive illness. nical trials have provided evidence that continuation treatment with PAXIL in patients with derate to moderately severe depressive disorder is effective for at least 6 months. **ssive-compulsive Disorder:** PAXIL (paroxetine) is indicated for the symptomatic atment of obsessive-compulsive disorder (OCD). The obsessions or compulsions must be perienced as intrusive, markedly distressing, time-consuming, or interfering significantly with person's social or occupational functioning. **Panic Disorder:** PAXIL (paroxetine) is indicated he symptomatic treatment of patients with Panic Disorder, with or without agoraphobia. e effectiveness of PAXIL in long-term use (i.e. for more than 12 weeks) has not yet been ablished in controlled trials for OCD and panic disorder. Therefore, the physician who elects use PAXIL for extended periods in these diseases should periodically re-evaluate the long- m usefulness of the drug for individual patients.

NTRAINDICATIONS: Hypersensitivity: PAXIL (paroxetine) is contraindicated in patients who known to be hypersensitive to the drug. **Monoamine Oxidase Inhibitors:** In patients eiving another serotonin reuptake inhibitor drug in combination with a MAO inhibitor, there ve been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, oclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental tus changes that include extreme agitation progressing to delirium and coma. These ictions have also been reported in patients who have recently discontinued that drug and ve begun treatment on a MAO inhibitor. Some cases presented with features resembling uroleptic malignant syndrome. Therefore, PAXIL should not be used in combination with AO inhibitors or within 2 weeks of terminating treatment with MAO inhibitors. Treatment with XIL should then be initiated cautiously and dosage increased gradually until optimal nonse is reached. MAO inhibitors should not be introduced within 2 weeks of cessation of rapy with PAXIL.

ECAUTIONS: Suicide: The possibility of a suicide attempt is inherent in depression and may rsist until remission occurs. Therefore, high risk patients should be closely supervised oughout therapy and with appropriate consideration should be given to the possible need for spitalization. In order to minimize the opportunity for overdosage, prescriptions for PAXIL roxetine) should be written for the smallest quantity of drug consistent with good patient nagement. **Seizures:** During clinical trials, the overall incidence of seizures was 0.15% in ients treated with PAXIL. However, patients with a history of convulsive disorders were luded from these studies. Caution is recommended when the drug is administered to ients with a history of seizures. The drug should be discontinued in any patient who velops seizures. **Activation of Mania/Hypomania:** During clinical testing in depressed ients, approximately 1% of PAXIL- treated patients experienced manic reactions. When olar patients were considered as a sub-group the incidence of mania was 2%. As with other ective Serotonin Reuptake Inhibitors (SSRIs), PAXIL should be used with caution in patients h a history of mania. **Occupational Hazards:** Although paroxetine did not cause sedation or erfere with psychomotor performance in placebo-controlled studies in normal subjects, ients should be advised to avoid driving a car or operating hazardous machinery until they reasonably certain that PAXIL does not affect them adversely. **Cardiac Conditions:** PAXIL es not generally produce clinically significant changes in blood pressure, heart rate or ECG. XIL has not been evaluated or used to any appreciable extent in patients with a recent history myocardial infarction or unstable heart disease. Hence, the usual precautions should be served in such patients. **Electroconvulsive Therapy (ECT):** The efficacy and safety of the ncurrent use of PAXIL and ECT have not been studied. **Use in Elderly:** Administration of XIL to the elderly is associated with increased plasma levels and prolongation of the mination half life relative to younger adults. (See Human Pharmacokinetics). Elderly patients uld be initiated and maintained at the lowest daily dose of paroxetine which is associated h clinical efficacy.

proximately 800 elderly patients (≥65 years) have been treated with PAXIL in worldwide marketing clinical trials. The pattern of adverse experiences in the elderly was comparable to t in younger patients. **Children:** The safety and effectiveness of PAXIL in children under 18 rs of age have not been established. **Pregnancy and Lactation:** Although animal studies ve not shown any teratogenic or selective embryotoxic effects, the safety of PAXIL in human gnancy has not been established. PAXIL should not be used during pregnancy unless the ential benefit to the patient outweighs the possible risk to the fetus.

concentrations of paroxetine detected in the breast milk of lactating women are similar to ne in plasma. Lactating women should not nurse their infants while receiving paroxetine. **nal Impairment:** Since PAXIL is extensively metabolized by the liver, excretion of unchanged g in urine is a minor route of elimination. However, single dose pharmacokinetic studies in jects with clinically significant renal impairment suggest that plasma levels of paroxetine are vated in such subjects. Paroxetine should therefore be used with caution and the dosage tricted to the lower end of the range in patients with clinically significant renal impairment. **patic Impairment:** Pharmacokinetic studies of PAXIL in subjects with clinically significant atic impairment suggest that prolongation of the elimination half-life and increased plasma els can be expected in this patient group. PAXIL should be used with caution and dosages tricted to the lower end of the range in patients with clinically significant hepatic impairment.

UG INTERACTIONS: Monoamine Oxidase Inhibitors: See CONTRAINDICATIONS.

ns Metabolized by Cytochrome P450(IID6): Like other selective serotonin re-uptake ibitors, paroxetine inhibits the specific hepatic cytochrome P450 isozyme (IID6) which is ponsible for the metabolism of debrisoquine and sparteine. Poor metabolizers of risoquine/sparteine represent approximately 5-10% of Caucasians. The median C_{min} (ss) PAXIL (20 mg daily) at steady state in poor metabolizers (n=8) was almost triple that orted for extensive metabolizers (n=9).

ough the full clinical significance of this effect has not been established, inhibition of IID6 can d to elevated plasma levels of co-administered drugs which are metabolized by this isozyme. wo studies, daily dosing of PAXIL (20 mg qd) under steady state conditions increased the owing mean pharmacokinetic parameters for a single (100 mg) dose of desipramine in ensive metabolizers: C_{max} (2 fold), AUC (6 fold), and $T_{1/2}$ (3-5 fold). Concomitant steady- e PAXIL treatment did not result in any further impairment of desipramine elimination in v metabolizers. Insufficient information is available to provide recommendations on the essary dosage adjustments for tricyclic antidepressants or PAXIL, if these drugs are to be d in combination.

comitant use of PAXIL with other drugs metabolized by IID6 has not been formally studied may require lower doses than usually prescribed for either PAXIL or the other drug. Drugs tabolized by cytochrome P450 (IID6) include certain tricyclic antidepressants (e.g. triptyline, amitriptyline, imipramine and desipramine), selective serotonin reuptake inhibitors . fluoxetine), phenothiazine neuroleptics (e.g. perphenazine and thioridazine) and Type IC arrhythmics (e.g. propafenone and flecainide). **CNS Drugs:** Experience in a limited number healthy subjects has shown that PAXIL does not increase the sedation and drowsiness ociated with haloperidol, amylbarbitone or oxazepam, when given in combination. Since the cts of concomitant administration of PAXIL with neuroleptics have not been studied, the use PAXIL with these drugs should be approached with caution. **Food/Antacids:** The absorption pharmacokinetics of PAXIL are not affected by food or antacids. **Cardiovascular Drugs:** tiple dose treatment with PAXIL 30 mg/day has little or no effect on the steady-state rmacokinetics of digoxin (0.25 mg qd) or propanolol (80 mg bid). **Anticoagulants:** PAXIL should be administered with great caution to patients receiving oral anticoagulants. Preliminary data suggest that a pharmacodynamic interaction between PAXIL and warfarin may result in increased bleeding in the presence of unaltered prothrombin times. **Microsomal Enzyme Inhibition/Induction:** The metabolism and pharmacokinetics of PAXIL may be affected by the induction or inhibition of drug metabolizing enzymes.

Steady state levels of PAXIL (30 mg daily) were elevated by about 50% when cimetidine (300 mg tid), a known drug metabolizing enzyme inhibitor, was co-administered to steady-state. Consideration should be given to using doses of PAXIL towards the lower end of the range when co-administered with known drug metabolizing enzyme inhibitors.

Co-administration of a single 30 mg dose of paroxetine to subjects receiving chronic daily dosing with 300 mg phenytoin, a known metabolizing enzyme inducer, is associated with decreased plasma levels of paroxetine (AUC reduced approximately 30%) and an increased incidence of adverse experiences. When a single 300 mg dose of phenytoin was administered to subjects receiving chronic daily dosing with 30 mg paroxetine the mean AUC of phenytoin was reduced by 12%. No initial dosage adjustment of PAXIL is considered necessary when the drug is to be co-administered with known drug metabolizing enzyme inducers. Any subsequent dosage adjustment should be guided by clinical effect. **Alcohol:** The concomitant use of PAXIL and alcohol has not been studied and is not recommended. Patients should be advised to avoid alcohol while taking PAXIL.

Tryptophan can be metabolized to serotonin. As with other serotonin reuptake inhibitors, the use of PAXIL together with tryptophan may result in adverse reactions consisting primarily of headache, nausea, sweating and dizziness. Consequently, concomitant use of PAXIL with tryptophan is not recommended.

Co-administration of PAXIL with anticonvulsants may be associated with an increased incidence of adverse experiences.

Chronic daily dosing with phenobarbital (100 mg qid for 14 days) decreased the systemic availability of a single 30 mg dose of paroxetine in some subjects. The AUC and $T_{1/2}$ of PAXIL were reduced by an average of 25% and 38% respectively compared to PAXIL administered alone. The effect of PAXIL on phenobarbital pharmacokinetics was not studied. No initial PAXIL dosage adjustment is considered necessary when co-administered with phenobarbital; any subsequent adjustment should be guided by clinical effect. PAXIL has been reported to increase the systemic bioavailability of procyclidine. Steady state plasma levels of procyclidine (5 mg daily) were elevated by about 40% when 30 mg paroxetine was co-administered to steady-state. **Drugs Highly Bound to Plasma Protein:** Paroxetine is highly bound to plasma protein, therefore administration of PAXIL to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug, potentially resulting in adverse events. Conversely, adverse effects could result from displacement of paroxetine by other highly bound drugs.

In a study of depressed patients stabilized on lithium, no pharmacokinetic interaction between paroxetine and lithium was observed. However, since there is limited experience in patients, the concurrent administration of PAXIL and lithium should be undertaken with caution.

A multiple dose study of the interaction between PAXIL and diazepam showed no alteration in the pharmacokinetics of PAXIL that would warrant changes in the dose of PAXIL for patients receiving both drugs. The effects of PAXIL on the pharmacokinetics of diazepam were not evaluated.

ADVERSE REACTIONS: Commonly Observed: The most commonly observed adverse experiences associated with the use of PAXIL (paroxetine) in clinical trials and not seen at an equivalent incidence among placebo-treated patients were: nausea, somnolence, sweating, tremor, asthenia, dizziness, dry mouth, insomnia, constipation, diarrhea, decreased appetite and male sexual dysfunction. **Adverse Events Leading to Discontinuation of Treatment:** 21% of approximately 4000 patients who received PAXIL in worldwide clinical trials in depression discontinued treatment due to an adverse experience. 11.8% (64/542) and 9.4 % (44/469) respectively of patients treated with PAXIL discontinued treatment because of adverse events. The most common events leading to discontinuation (reported by 1% or more of subjects) included: asthenia, headache, nausea, somnolence, insomnia, agitation, tremor, dizziness, constipation, impotence and abnormal ejaculation. **Adverse Effects following Discontinuation of Treatment:** Some patients may experience physical symptoms such as dizziness/lightheadedness, gastrointestinal complaints, headache, agitation/restlessness and sleep disturbance during the period following the discontinuation of paroxetine treatment. These events are generally mild and transient. **Adverse Experience Reports:** Multiple doses of PAXIL were administered to 4126 subjects in clinical trials for depression, 542 subjects in clinical trials for OCD and 469 subjects in clinical trials for Panic Disorder. Untoward experiences associated with this exposure were recorded by clinical investigators using descriptive terminology of their own choosing.

Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse experiences without first grouping similar types of untoward experiences into a limited (i.e., reduced) number of standardized experience categories.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly the cited incidences cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited frequencies do however provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence rate in the population studied. Reported adverse experiences were classified using a COSTART-based Dictionary terminology for the depression trials and an ADECS (a modified COSTART dictionary) for OCD and panic disorder trials.

In the tabulations which follow, a COSTART or modified COSTART-based Dictionary terminology has been used to classify reported adverse experiences. The frequencies presented therefore represent the portion of the 4126,.542 and 469 PAXIL-exposed individuals in depression, OCD and pPanic trials, respectively, who experienced an event of the type cited on at least one occasion while receiving PAXIL. Experiences are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent experiences are defined as those occurring on one or more occasion in at least 1/100 patients; infrequent adverse experiences are those occurring in less than 1/100 but at least 1/1000 patients; rare experiences are those occurring in less than 1/1000 patients.

It is important to emphasize that although the experiences reported did occur during treatment with PAXIL, they were not necessarily caused by it.

Body as a Whole: Frequent: Malaise, pain. **Infrequent:** Allergic reaction, chills, face edema, infection, moniliasis, neck pain, overdose. **Rare:** Abnormal laboratory value, abscess, adrenergic syndrome, cellulitis, chills and fever, cyst, hernia, intentional overdose, neck rigidity, pelvic pain, peritonitis, substernal chest pain, ulcer. **Cardiovascular System: Frequent:** Hypertension, syncope, tachycardia. **Infrequent:** Bradycardia, conduction abnormalities, electrocardiogram abnormal, hypotension, migraine, ventricular extrasystoles. **Rare:** Angina pectoris, arrhythmia, atrial arrhythmia, atrial fibrillation, bundle branch block, cerebral ischemia, cerebrovascular accident, congestive heart failure, extrasystoles, low cardiac output, myocardial infarct, myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombosis, varicose vein, vascular headache. **Dermatological: Frequent:** Pruritus. **Infrequent:** Acne, alopecia, dry skin, ecchymosis, eczema, furunculosis, herpes simplex, urticaria. **Rare:** Angioedema, contact dermatitis, erythema nodosum, herpes zoster, maculopapular rash, photosensitivity, skin discolouration, skin ulcer, skin hypertrophy. **Endocrine: Rare:** Diabetes mellitus, hyperthyroidism, hypothyroidism, thyroiditis. **Gastrointestinal: Frequent:** Nausea and vomiting. **Infrequent:** Bruxism, buccal cavity disorders, dysphagia, eructation, gastroenteritis, gastrointestinal flu, glossitis, increased salivation, liver function tests abnormal, mouth ulceration, vomiting and diarrhea, rectal hemorrhage. **Rare:** Aphthous stomatitis, bloody diarrhea, bulimia, colitis, duodenitis, esophagitis, fecal impaction, fecal incontinence, gastritis, gingivitis, hematemesis, hepatitis, ileus, jaundice, melena, peptic ulcer, salivary gland enlargement, stomach ulcer, stomatitis, tongue edema, tooth caries. **Hematologic and Lymphatic: Infrequent:** Anemia, leukopenia, lymphadenopathy, purpura, WBC abnormality. Rare: Eosinophilia, iron deficiency anemia, leukocytosis, lymphedema, lymphocytosis, microcytic anemia, monocytosis, normocytic anemia. **Metabolic and Nutritional: Frequent:** Weight gain, weight loss. **Infrequent:** Edema, hyperglycemia, peripheral edema, thirst. **Rare:** Alkaline phosphatase increased, bilirubinemia, dehydration, gout, hypercholesteremia, hypocalcemia, hypoglycemia, hypokalemia, hyponatremia, obesity, SGOT increased, SGPT increased. **Musculoskeletal: Infrequent:** Arthralgia, arthritis, traumatic fracture. **Rare:** Arthrosis, bursitis, cartilage disorder, myositis, osteoporosis, tetany. **Nervous System: Frequent:** CNS stimulation, concentration impaired, depression, emotional lability, vertigo. **Infrequent:** Akinesia, alcohol abuse, amnesia, ataxia, convulsion, depersonalization, hallucinations, hyperkinesia, hypertonia, incoordination, lack of emotion, manic reaction, paranoid reaction, thinking abnormal, hypesthesia. **Rare:** Abnormal electroencephalogram, abnormal gait, antisocial reaction, choreoathetosis, circumoral paresthesia, delirium, delusions, diplopia, drug dependence, dysarthria, dyskinesia, dystonia, euphoria, fasciculations, grand mal convulsion, hostility, hyperalgesia, hypokinesia, hysteria, libido increased, manic depressive reaction, meningitis, myelitis, neuralgia, neuropathy, nystagmus, psychosis, psychotic depression, reflexes increased, stupor, withdrawal syndrome. **Respiratory System: Frequent:** Cough increased, rhinitis. **Infrequent:** Asthma, bronchitis, dyspnea, epistaxis, hyperventilation, pneumonia, respiratory flu, sinusitis. **Rare:** Hiccup, lung fibrosis, sputum increased, voice alteration. **Special Senses: Infrequent:** Abnormality of accommodation, conjunctivitis, ear pain, eye pain, mydriasis, otitis media, tinnitus. **Rare:** Amblyopia, cataract specified, conjunctival edema, corneal lesion, corneal ulcer, exophthalmos, eye hemorrhage, glaucoma, hyperacusis, otitis externa, photophobia, retinal hemorrhage, taste loss, anisocoria, deafness, keratoconjunctivitis. **Urogenital system: Infrequent:** Abortion*, amenorrhea*, breast pain*, cystitis, dysmenorrhea*, dysuria, menorrhagia*, nocturia, polyuria, urinary incontinence, urinary retention, urinary tract infection, urinary urgency, vaginitis*. **Rare:** Breast atrophy*, female lactation*, hematuria, kidney calculus, kidney function abnormal, kidney pain, mastitis*, nephritis, oliguria, urethritis, urine abnormality, vaginal moniliasis*.

* Incidence corrected for gender.

SYMPTOMS AND TREATMENT OF OVERDOSAGE: Overdose attempts have been reported with PAXIL (paroxetine; up to 2000 mg) alone and in combination with other agents during premarketing clinical trials. In cases where PAXIL was used alone, no deaths have occurred and recovery was medically uneventful.

Symptoms of overdosage with PAXIL include nausea, vomiting, drowsiness, sinus tachycardia, tremor, dilated pupils, dry mouth and irritability. There are no reports of ECG abnormalities, coma or convulsions following overdosage with PAXIL alone.

No specific antidote is known. Treatment should consist of those general measures employed in the management of overdose with any antidepressant. Establish and maintain an airway; ensure adequate oxygenation and ventilation. The stomach should be emptied either by the induction of emesis, lavage or both. Following evacuation, 20 to 30 grams of activated charcoal may be administered every 4 to 6 hours during the first 24 hours after ingestion. An ECG should be taken and monitoring of cardiac function instituted if there is any evidence of abnormality. Supportive care with frequent monitoring of vital signs and careful observation is indicated. Due to the large volume of distribution of PAXIL, forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit.

A specific caution involves patients taking or recently having taken PAXIL who might ingest by accident or intent excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the parent tricyclic and its active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation.

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose.

DOSAGE AND ADMINISTRATION: General: PAXIL should be administered once daily in the morning and may be taken with or without food. The tablet should be swallowed rather than chewed. **Dose Adjustments:** Based on pharmacokinetic parameters, steady-state paroxetine plasma levels are achieved over a 7-14 day interval. Hence, dosage adjustments in 10 mg increments should be made at 1-2 week intervals or according to clinician judgment. **Maintenance:** During long term therapy for any indication, the dosage should be maintained at the lowest effective level. **Discontinuation:** Some patients may experience physical symptoms following discontinuation of treatment. Although it is unknown if gradual discontinuation will reduce or prevent these symptoms, a gradual tapering of dosage should be considered when treatment is to be discontinued (See 'Adverse Effects following Discontinuation of Treatment' in the Adverse Events section).

DEPRESSION: Usual Adult Dose: The administration of PAXIL (paroxetine) should be initiated at 20 mg daily. For most patients, 20 mg daily will also be the optimum dose. The therapeutic response may be delayed until the third or fourth week of treatment.

Dose Range: For those patients who do not respond adequately to the 20 mg daily dose, a gradual increase in dosage up to 40 mg daily may be considered. The maximum recommended daily dose is 50 mg.

OBSESSIVE-COMPULSIVE DISORDER: Usual Adult Dose: The administration of PAXIL (paroxetine) should be initiated at 20 mg/day. The recommended dose of PAXIL in the treatment of OCD is 40 mg daily.

Dose Range: For those patients who do not respond adequately to the 40 mg daily dose, a gradual increase in dosage may be considered. The maximum recommended daily dose is 60 mg.

PANIC DISORDER: Usual Adult Dose: The recommended starting dose of PAXIL (paroxetine) in the treatment of Panic Disorder is 10 mg/day. The recommended dose of PAXIL in the treatment of Panic Disorder is 40 mg daily.

Dose Range: For those patients who do not respond adequately to the 40 mg daily dose, a gradual increase in dosage may be considered. The maximum recommended daily dose is 60 mg.

SPECIAL PATIENT POPULATIONS: For any indication: Elderly: A lower initial dose may be considered for elderly and/or debilitated patients. Increases in The dose may be made increased if indicated up to a maximum of 40 mg daily.

Children: The use of PAXIL in children under 18 years of age is not recommended as safety and efficacy have not been established in this population.

Renal/Hepatic Impairment: PAXIL should be used with caution in patients with renal or hepatic impairment. Dosage should be restricted to the lower end of the range in patients with clinically significant renal or hepatic impairment (See Precautions). A maximum dose of 40 mg should not be exceeded.

AVAILABILITY OF DOSAGE FORMS: PAXIL (paroxetine) is available as film coated, oval biconvex tablets containing paroxetine hydrochloride equivalent to 20 mg (pink tablets), 30 mg (blue tablets) paroxetine free base. The tablets have the product name engraved on one side and strength engraved on the other side.The 20 mg tablets are bisected. Available in package sizes of:
20 mg - 100's
30 mg - 30's

Full Prescribing Information available to Health Practitioners upon request.

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Oakville, Ont. L6H 5V2

LESCOL*

FLUVASTATIN SODIUM

PRESCRIBING INFORMATION

20 mg and 40 mg capsules

THERAPEUTIC CLASSIFICATION – Lipid metabolism regulator

ACTIONS AND CLINICAL PHARMACOLOGY – LESCOL* (fluvastatin sodium) is a synthetic HMG-CoA reductase inhibitor, and is hydrophilic. Fluvastatin sodium is a racemate of two erythro enantiomers of which one exerts the pharmacological activity. LESCOL is a competitive inhibitor of HMG-CoA reductase, which is responsible for the conversion of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) to mevalonate, a precursor of sterols, including cholesterol. The inhibition of cholesterol biosynthesis reduces the cholesterol in hepatic cells, which stimulates the synthesis of LDL receptors and thereby increases the uptake of LDL particles. The ultimate result of these mechanisms is a reduction of the plasma total cholesterol (total-C) and low density lipoprotein cholesterol (LDL-C) concentrations.

INDICATIONS AND CLINICAL USE – The primary therapeutic indication for LESCOL (fluvastatin sodium) is as an adjunct to diet (at least equivalent to the American Heart Association [AHA] Step 1 Diet) in the treatment of elevated total cholesterol (total-C) and LDL-C levels in patients with primary hypercholesterolemia (Type IIa and IIb) whose response to dietary restriction of saturated fat and cholesterol and other non-pharmacological measures has not been adequate. Therapy with lipid-altering agents should be considered only after secondary causes for hyperlipidemia such as poorly controlled diabetes mellitus, hypothyroidism, nephrotic syndrome, dysproteinemias, obstructive liver disease, other medication, or alcoholism, have been excluded. Prior to initiation of LESCOL, a lipid profile should be performed to measure total-C, HDL-C and TG. For patients with TG < 4.52 mmol/L (< 400 mg/dL), LDL-C can be estimated using the following equation: LDL-C (mmol/L) = total-C - HDL-C - 0.37 TG. For TG levels > 4.52 mmol/L (> 400 mg/dL), this equation is less accurate and LDL-C concentrations should be determined by ultracentrifugation. In many hypertriglyceridemic patients, LDL-C may be low or normal despite elevated total-C. In such cases, as with other HMG-CoA reductase inhibitors, LESCOL is not indicated. Since the goal of treatment is to lower LDL-C, LDL-C levels should be used to initiate and assess treatment response. Only if LDL-C levels are not available, should the total-C be used to monitor therapy. LESCOL has not been studied in conditions where the major abnormality is elevation of chylomicrons, VLDL, or IDL (i.e. hyperlipoproteinemia Types I, III, IV, or V).

CONTRAINDICATIONS – Hypersensitivity to any component of this medication. LESCOL (fluvastatin sodium) is contraindicated in patients with active liver disease or unexplained, persistent clinically relevant elevations in serum transaminases (see WARNINGS). As with other drugs of this class, LESCOL is contraindicated during pregnancy and in nursing mothers (see PRECAUTIONS).

WARNINGS – As for other drugs of this class, the effect of fluvastatin-induced changes in lipoprotein levels, including reduction of serum cholesterol, on cardiovascular morbidity and mortality, or total mortality has not been established. Liver Enzymes: Biochemical abnormalities of liver function have been associated with HMG-CoA reductase inhibitors and other lipid-lowering agents. A small number of patients treated with LESCOL (fluvastatin sodium) in controlled trials (n = 17 of 1524; 1.1%) developed marked persistent elevations (to more than 3 times the upper limit of normal) of transaminase levels. Most of these abnormalities occurred within the first 6 weeks of treatment (time of occurrence ranging from 2 to 54 weeks). In patients in which the drug was discontinued (10/17), the transaminases levels usually declined rapidly to pretreatment levels. Two patients in which therapy was not interrupted, had transaminases elevations possibly related to the study drug; these abnormalities slowly resolved on continued therapy. In a long-term open label extension study, 5 of 824 (0.6%) patients exposed to LESCOL at a dose of 40 mg/day developed persistent transaminase elevations. Only two of these patients were discontinued from the study. The majority of these abnormal biochemical findings were asymptomatic. **It is recommended that liver function tests be performed within the first 12 weeks after initiation of treatment or after an increase in the dose, and periodically thereafter.** Liver enzyme changes generally occur in the first 3 months of treatment with LESCOL. Any patient on LESCOL complaining of flu-like symptoms, malaise, fatigue should be evaluated clinically and, if warranted, should have serum transaminases measured as these may be common presenting symptoms of serious liver damage. Patients who develop increased transaminase levels should be monitored with a second liver function evaluation to confirm the finding and be followed thereafter with frequent liver function tests until the abnormality(ies) return to normal. **Should an increase in ASAT or ALAT of three times the upper limit of normal or greater persist. LESCOL therapy should be discontinued.** Active liver disease or unexplained transaminase elevations are contraindications to the use of LESCOL (see CONTRAINDICATIONS). Caution should be exercised when LESCOL is administered to patients with a history of liver disease or heavy alcohol ingestion (see PHARMACOLOGY: Pharmacokinetics/ Metabolism). Such patients should be closely monitored. **Skeletal Muscle:** Rhabdomyolysis with renal dysfunction secondary to myoglobinuria has not been reported to date with LESCOL therapy. Myopathy (defined as muscle aching or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values to greater than 10 times the upper limit of normal) has been reported in one LESCOL treated patient to date, which was related to physical exertion. An additional case was reported in a patient receiving placebo. However, because these adverse events have been reported with other drugs of this class, the following cautions are advised. Myopathy should be considered in any patients with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK (greater than 10 times the upper limit of normal). Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. **LESCOL therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected.** LESCOL therapy should also be temporarily withheld in any patient experiencing an acute or serious condition predisposing to the development of renal failure secondary to rhabdomyolysis, e.g., sepsis; hypotension; major surgery; trauma, severe metabolic, endocrine, or electrolyte disorders; or uncontrolled epilepsy. An increased risk of myopathy has been reported with another HMG CoA reductase inhibitor (lovastatin) when administered concomitantly with cyclosporine, gemfibrozil, erythromycin, or niacin. There is limited experience to date with the use of LESCOL together with cyclosporine. Myopathy has not been observed in clinical trials involving small numbers of patients who were treated with LESCOL together with niacin. Although the use of fibrates alone or in combination with lovastatin has been occasionally associated with myopathy, in a crossover study to investigate the pharmacokinetic interaction of LESCOL and bezafibrate in 30 volunteers no myopathy was observed.

PRECAUTIONS – General: Before instituting therapy with LESCOL (fluvastatin), an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, weight reduction in overweight and obese patients, and to treat other underlying medical problems (see INDICATIONS AND CLINICAL USE). The patient should be advised to inform subsequent physicians of the prior use of LESCOL or any other lipid-lowering agent. **Homozygous Familial Hypercholesterolemia**: LESCOL (fluvastatin sodium) has not been evaluated in patients with rare homozygous familial hypercholesterolemia. HMG-CoA reductase inhibitors are reported to be less or not effective in patients with rare homozygous familial hypercholesterolemia, possibly because these patients have few functional LDL receptors. Additionally, studies with other HMG-CoA reductase inhibitors indicate that such treatment appears more likely to raise serum transaminases in these homozygous patients. **Effect on lipoprotein(A) [Lp(a)]:** In some patients the beneficial effect of lowered total cholesterol and LDL cholesterol levels may be partly blunted by a concomitant increase in the Lp(a) levels. Until further experience is obtained from controlled clinical trials, it is suggested, where feasible, that Lp(a) measurements be carried out in patients placed on therapy with LESCOL. **Effect on CoQ_{10} levels (Ubiquinone):** A significant decrease in plasma CoQ_{10} levels in patients treated with LESCOL and other statins has been observed in short-term clinical trials. The clinical significance of a potential long-term statin-induced deficiency of CoQ_{10} has not yet been established. **Severe Renal Impairment:** Caution is advised in patients with severe renal impairment. **Endocrine Function:** HMG-CoA reductase inhibitors interfere with cholesterol synthesis and as such might theoretically blunt adrenal and/or gonadal steroid production. LESCOL exhibited no effect upon non-stimulated cortisol levels, FSH (males only) or thyroid metabolism as assessed by TSH. Small declines in total testosterone have been noted in treated groups, but no commensurate elevation in LH occurred. However, the effects of HMG-CoA reductase inhibitors on male fertility have not been studied in an adequate number of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Patients treated with LESCOL who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients receiving other drugs (e.g. ketoconazole, spironolactone, or cimetidine) that may decrease the levels of endogenous steroid hormones. **Ophthalmic Evaluations**: Current data from clinical trials do not indicate an adverse effect of LESCOL on the human lens. However, long-term effects are not yet established and therefore periodic ophthalmological examinations are recommended taking into consideration that, in the absence of any drug therapy, an increase in the prevalence of lens opacities with time is expected as a result of aging. **Pregnancy:** LESCOL is contraindicated during pregnancy and in nursing mothers (see CONTRAINDICATIONS). Data on the use of LESCOL in pregnant women is limited. During the clinical program, a total of 5 women who were receiving LESCOL became pregnant and were discontinued from the studies. Of these 5 women, 2 gave birth to healthy babies, one experienced an ectopic pregnancy which was attributed to a severely scarred fallopian tube; and one spontaneously aborted. The outcome for the fifth patient is not yet known. Atherosclerosis is a chronic process and discontinuation of lipid metabolism regulators during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. LESCOL should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the patient becomes pregnant while taking this class of drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus (see CONTRAINDICATIONS). **Nursing Mothers:** Because of the potential for serious adverse reactions in nursing infants, women receiving LESCOL should not breast-feed (see CONTRAINDICATIONS). **Pediatric Use:** Only limited experience with the use of HMG-CoA reductase inhibitors is available in children; however, there is no experience to date with the use of LESCOL in such patients. **Geriatric Use:** The effect of age on the pharmacokinetics of LESCOL was evaluated. Results indicate that for the general patient population plasma concentrations of fluvastatin sodium do not vary either as a function of age or gender. (See also PHARMACOLOGY: Pharmacokinetics/ Metabolism.)

DRUG INTERACTIONS – A drug interactive effect (pharmacokinetic and/or clinical) has been shown for the following drugs in combination with LESCOL: *Cholestyramine:* Administration of LESCOL concomitantly 2 to 4 hours after cholestyramine, results in fluvastatin decreases of more than 50% for the fluvastatin AUC and 50-80% for the fluvastatin C_{max}. However, administration of LESCOL 4 hours after cholestyramine resulted in a clinically significant additive effect in reducing total-C and LDL-C compared with that achieved with either component drug (see DOSAGE AND ADMINISTRATION). *Gemfibrozil/Fenofibrate/Niacin:* Myopathy, including rhabdomyolysis, has occurred in patients who were receiving co-administration of other HMG-CoA reductase inhibitors with fibric acid derivatives and niacin, particularly in subjects with pre-existing renal insufficiency. (see WARNINGS: Skeletal Muscle) *Cimetidine/Ranitidine/ Omeprazole:* Concomitant administration of LESCOL with cimetidine, ranitidine and omeprazole results in a significant increase in the fluvastatin C_{max} (43%, 70% and 50%, respectively) and AUC (24 to 33%), with an 18 to 23% decrease in apparent oral plasma clearance (Cl/F). *Digoxin:* In a crossover study involving 18 patients chronically receiving digoxin, concomitant administration of a single 40 mg dose of LESCOL had no effect on digoxin AUC and small but clinically insignificant increases in the digoxin C_{max} and urinary clearance were noted. *Rifampicin:* Administration of LESCOL to subjects pretreated with rifampicin results in significant reduction in C_{max} (59%) and AUC (51%) of fluvastatin, with a large increase (95%) in plasma clearance. In pharmacokinetic studies and in retrospective analysis of the concomitant medications used during clinical studies, LESCOL did not show an interactive effect with the following drugs: *Antipyrine:* Administration of LESCOL does not influence the metabolism and excretion of antipyrine, either by induction or inhibition. Antipyrine is a model for drugs metabolized by the microsomal hepatic enzyme system; therefore, interactions with other drugs metabolized by this mechanism are not expected. *Niacin/Propranolol:* Concomitant administration of LESCOL with niacin or propranolol has no effect on the bioavailability of fluvastatin sodium. *Warfarin:* In vitro protein binding studies demonstrated no interaction at therapeutic concentrations. However, since other drugs of this class have been shown to enhance the anticoagulant effect of warfarin, caution is advised when administering warfarin concomitantly with LESCOL. *Other Concomitant Therapy:* Although specific interaction studies were not performed, in clinical studies, LESCOL was used concomitantly with angiotensin-converting enzyme (ACE) inhibitors, beta blockers, calcium-channel blockers, antacids, diuretics and nonsteroidal anti-inflammatory drugs (NSAIDs) without evidence of clinically significant interactions. Although no conclusive studies have been done to date with LESCOL, interactions with the following drugs have been reported with other HMG-CoA reductase inhibitors: *Immunosuppressive Drugs, Erythromycin:* See WARNINGS: Skeletal Muscle. **Laboratory interactions** : The HMG-CoA reductase inhibitors may cause elevation of creatinine phosphokinase and transaminase levels (see WARNINGS). In the differential diagnosis of chest pain in a patient on LESCOL, cardiac and noncardiac fractions of these enzymes should be determined.

ADVERSE REACTIONS – In the controlled clinical studies and their open extensions, 1% of 1881 patients were discontinued due to adverse experiences attributable to LESCOL (fluvastatin sodium) (mean exposure approx. 14 months ranging in duration from one to more than 24 months). When adjusted for duration of exposure this incidence was slightly less for patients receiving LESCOL compared to those on placebo (0.9% vs. 1.3%). Adverse reactions were usually mild and transient and similar in incidence to placebo. Common adverse experiences possibly attributable to LESCOL at the recommended dose range of 20-40 mg/day which occurred at a > 1% frequency are listed on the chart.

ADVERSE EVENT	LESCOL (%) (n = 620)+	Placebo (%) (n = 411)
Gastrointestinal		
Dyspepsia	6.6%	3.6%
Diarrhea	3.2%	3.2%
Abdominal Pain	3.9%	2.4%
Nausea	2.7%	1.5%
Flatulence	1.6%	4.1%
Constipation	1.8%	3.6%
Musculoskeletal		
Arthropathy	1.5%	1.5%
Back pain	1.3%	1.7%
Myalgia	1.1%	1.5%
Central Nervous System		
Dizziness	1.8%	2.2%
Abnormal vision	1.3%	2.4%
Psychiatric		
Insomnia	1.8%	1.2%
Respiratory		
Upper respiratory infection	1.1%	2.9%
Integumentary		
Rash	2.1%	2.9%
Miscellaneous		
Headache	3.5%	3.6%
Fatigue	2.3%	2.9%

+N = 620 includes all patients who received LESCOL in the core controlled clinical studies

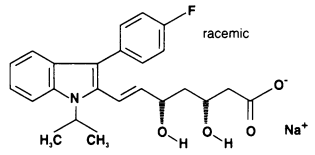
The following effects have been reported with drugs of this class: *Skeletal:* myopathy, rhabdomyolysis (see WARNINGS), muscle cramping/ pain. *Neurological:* paresthesia, peripheral neuropathy, psychiatric disturbances/anxiety. *Hypersensitivity Reactions:* An apparent hypersensitivity syndrome has been reported rarely with other HMG-CoA reductase inhibitors and has included one or more of the following features: anaphylaxis, angioedema, lupus erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive antinuclear antibody (ANA), erythrocytes sedimentation rate (ESR) increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiform, including Stevens-Johnson syndrome. *Gastrointestinal:* hepatitis, cholestatic jaundice, anorexia, vomiting. *Skin:* alopecia. *Miscellaneous:* Asthenia, sweating, hot flashes.

SYMPTOMS AND TREATMENT OF OVERDOSAGE – The maximum single oral dose of LESCOL (fluvastatin sodium) received by healthy volunteers was 60 mg. No clinically significant adverse experiences were seen at this dose. There has been a single report of two children, one 2 years old and the other 3 years of age, either of whom may have possibly ingested LESCOL. The maximum amount of LESCOL ingested was 80 mg (4 x 20 mg capsules). Vomiting was induced by ipecac in both children and no capsules were noted in their emesis. Neither child experienced any adverse symptoms and both recovered from the incident without problems. No specific information on the treatment of overdosage can be recommended. Should an accidental overdose occur, treat symptomatically and institute supportive measures as required. The dialyzability of LESCOL and its metabolites in man is not known at present.

DOSAGE AND ADMINISTRATION – Prior to initiating LESCOL (fluvastatin sodium), the patient should be placed on a standard cholesterol-lowering diet (at least equivalent to the American Heart Association [AHA] Step 1 Diet), which should be continued during treatment. If appropriate, a program of weight control and physical exercise should be implemented. The recommended starting dose is 20 mg once daily at bedtime. The recommended dosing range is 20-40 mg/day as a single dose in the evening. As with other drugs of this class, splitting the larger dose into a BID regimen provides a modest improvement in LDL-C response. LESCOL may be taken without regard to meals, since there are no apparent differences in the lipid lowering effects of LESCOL administered with the evening meal or 4 hours after the evening meal. Since the maximal reductions in LDL-C are seen within 4 weeks of administration of a given dose, periodic lipid determinations should be performed during this time, and periodically thereafter, with dosage adjusted to a maximum of 40 mg/day according to the patient's response to therapy. The therapeutic effect of LESCOL is maintained with prolonged administration. **Cholesterol levels should be monitored periodically and consideration should be given to reducing the dosage of LESCOL if cholesterol levels fall below the targeted range, such as that recommended by the second report of the U.S. National Cholesterol Education Program (NCEP) Concomitant Therapy:** The lipid lowering effects of LESCOL on total cholesterol and LDL cholesterol are enhanced when combined with a bile-acid binding resin. When administering a bile-acid resin (e.g., cholestyramine) and fluvastatin sodium concomitantly, LESCOL should be administered at bedtime, at least 4 hours following the resin to obtain a maximal lipid lowering effect. (See PRECAUTIONS, DRUG INTERACTIONS). **Dosage in Patients with Renal Insufficiency:** Since LESCOL is cleared hepatically with less than 5% of the administered dose excreted into the urine, dose adjustments for mild to moderate renal impairment are not deemed to be necessary. Caution should be exercised with severe renal impairment (see PRECAUTIONS).

PHARMACEUTICAL INFORMATION – Drug Substance: Proper Name: fluvastatin sodium – **Chemical Name:** [R*,S*-(E)]-(±)-7-[3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]-3,5-dihydroxy -6-heptenoic acid, monosodium salt – **Empirical Formula:** $C_{24}H_{25}FNO_4 \cdot Na$ – **Molecular Weight:** 433.46.

Structural Formula:



Description: Fluvastatin sodium is a white to pale yellow, hygroscopic powder soluble in water, ethanol and methanol. The pKa value is approximately 5.5. The pH of a 1% solution (w/v) varies between 8.2-10.0 due to trace amounts of residual sodium hydroxide or carbonates. The octanol/water partition coefficient is 6.8. **Composition: Active Ingredient:** fluvastatin sodium. **Inactive Ingredients:** sodium bicarbonate, calcium carbonate, microcrystalline cellulose, pregelatinized starch, talc, magnesium stearate, gelatin, iron oxide red, iron oxide yellow, iron oxide black, titanium dioxide, silicon dioxide, sodium laurel sulphate, benzyl alcohol, sodium propionate, edetate calcium disodium, carboxymethyl cellulose sodium, butyl paraben, propyl paraben, methyl paraben, shellac, polyvinylpyrrolidone, ethyl alcohol, isopropyl alcohol, propylene glycol, n-butyl alcohol, sodium hydroxide, ammonium hydroxide.

STABILITY AND STORAGE RECOMMENDATIONS – Store between 15 and 30°C in a tight container. Protect from light and humidity.

AVAILABILITY OF DOSAGE FORMS – LESCOL Capsules 20 mg: Each brown opaque cap and light brown opaque body gelatin capsule contains 20 mg fluvastatin (from 21.06 mg fluvastatin sodium). Sandoz triangle S printed twice and "20" in white ink on the cap; "Lescol" and product logo in red ink on the body. Available in bottles of 100.

LESCOL Capsules 40 mg: Each brown opaque cap and gold opaque body gelatin capsule contains 40 mg fluvastatin (from 42.12 mg fluvastatin sodium). Sandoz triangle S printed twice and "40" in white ink on the cap: "Lescol" and product logo in red ink on the body. Available in bottles of 100.

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Product Monograph available on request.

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TYLENOL* acetaminophen

A LOGICAL FIRST CHOICE

ACTIONS:
Acetaminophen is an analgesic and antipyretic.

INDICATIONS:
TYLENOL* acetaminophen is indicated for the relief of pain and fever. Also as an analgesic/antipyretic in the symptomatic treatment of colds.

CONTRAINDICATION:
Hypersensitivity to acetaminophen.

ADVERSE EFFECTS:
In contrast to salicylates, gastrointestinal irritation rarely occurs with acetaminophen. If a rare hypersensitivity reaction occurs, discontinue the drug. Hypersensitivity is manifested by rash or urticaria. Regular use of acetaminophen has shown to produce a slight increase in prothrombin time in patients receiving oral anticoagulants, but the clinical significance of this effect is not clear.

PRECAUTIONS AND TREATMENT OF OVERDOSE:
Resuscitation and supportive care must proceed as for any other potentially serious overdose. In acute overdose, serum levels of acetaminophen are meaningful in predicting those patients likely to develop serious hepatic toxicity. They must be drawn between 4 and 24 hours post overdose and the values plotted on the Matthew-Rumack Nomogram. N-acetylcysteine (N.A.C.) is a highly effective antidote for acetaminophen poisoning. Do not delay administration of N.A.C. either by parenteral or oral routes if the ingested dose is likely to be toxic (> 150 mg/kg ingested) or if serum levels are in the toxic range on the Nomogram. N.A.C. must be administered prior to the 24th hour post overdose to be protective. Further details on therapy of acetaminophen overdose are available by calling your regional Poison Control Centre.

DOSAGE:
Adults: 650 to 1000 mg every 4 to 6 hours, not to exceed 4000 mg in 24 hours.

SUPPLIED:
TYLENOL* Caplets 325 mg: Each white caplet, scored on one side and engraved "TYLENOL" other side, contains 325 mg acetaminophen. Available in bottles of 24†, 50†, 100† and 200††caplets.

TYLENOL* Tablets 325 mg: Each round, white tablet, scored on one side and engraved "TYLENOL" other side, contains 325 mg acetaminophen. Available in bottles of 24†, 50†, 100 and 500 tablets. Also available in vials of 12 tablets.

TYLENOL* Caplets 500 mg: Each white caplet, engraved "TYLENOL" on one side and "500" other side, contains 500 mg acetaminophen. Available in bottles of 24†, 50†, 100† and 150††caplets. Also available in vials of 10 caplets.

TYLENOL* Tablets 500 mg: Each round, white tablet, engraved "TYLENOL" one side, and "500" other side contains 500 mg acetaminophen. Available in bottles of 30†, 50 and 100† tablets. Also available in vials of 10 tablets.

TYLENOL* Gelcaps 500 mg: Each solid caplet-shaped tablet, coated with red gelatin on one end and yellow on the other, printed "TYLENOL/500" on each gelatin coated end, contains: 500 mg acetaminophen. Available in bottles of 24† and 50 gelcaps.

†Package is child-resistant. ††Easy to open.

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SPECIFY TWO EXTRA STRENGTH TYLENOL* acetaminophen

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TRIPHASIL®

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TRIPHASIL® 21 AND TRIPHASIL® 28 TABLETS: THERAPEUTIC CLASSIFICATION ORAL CONTRACEPTIVE

INDICATION Triphasil® Tablets are indicated for conception control. **CONTRAINDICATIONS 1.** History of/or actual thrombophlebitis or thromboembolic disorders. **2.** History of/or actual cerebrovascular disorders. **3.** History of/or actual myocardial infarction or coronary arterial disease. **4.** Active liver disease or history of/or actual benign or malignant liver tumours. **5.** Known or suspected carcinoma of the breast. **6.** Known or suspected estrogen-dependent neoplasia. **7.** Undiagnosed abnormal vaginal bleeding. **8.** Any ocular lesion arising from ophthalmic vascular disease, such as partial or complete loss of vision or defect in visual fields. **9.** When pregnancy is suspected or diagnosed.

WARNINGS

1. Predisposing Factors For Coronary Artery Diseases Cigarette smoking increases the risk of serious cardiovascular side effects and mortality. Birth control pills increase this risk, especially with increasing age. Convincing data are available to support an upper age limit of 35 years for oral contraceptive use in women who smoke. Other women who are independently at high risk for cardiovascular disease include those with diabetes, hypertension, abnormal lipid profile, or a family history of these. Whether OCs accentuate this risk is unclear. In low risk, non-smoking women of any age, the benefits of oral contraceptive use outweigh the possible cardiovascular risks associated with low dose formulations. Consequently, oral contraceptives may be prescribed for these women up to the age of menopause.

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. This risk increases with age and becomes significant in OC-users over 35 years of age. Women should be counseled not to smoke.

2. Discontinue medication at the earliest manifestation of: A. Thromboembolic and Cardiovascular Disorders such as: Thrombophlebitis, pulmonary embolism, cerebrovascular disorders, myocardial ischemia, mesenteric thrombosis, and retinal thrombosis. **B.** Conditions which predispose to Venous Stasis and to Vascular Thrombosis, e.g. immobilization after accidents or confinement to bed during long-term illness. Other non-hormonal methods of contraception should be used until regular activities are resumed. For use of oral contraceptives when surgery is contemplated, see "PRECAUTIONS." **C. Visual Defects, Partial or Complete. D. Papilledema, or Ophthalmic Vascular Lesions. E. Severe Headache of Unknown Etiology or Worsening of Pre-existing Migraine Headache.**

PRECAUTIONS

1. Physical Examination and Follow-up Before oral contraceptives are used, a thorough history and physical examination should be performed, including a blood pressure determination. Breasts, liver, extremities and pelvic organs should be examined. A Papanicolaou smear should be taken if the patient has been sexually active. The first follow-up examination should be done 3 months after oral contraceptives are prescribed. Thereafter, examinations should be performed at least once a year or more frequently if indicated. At each annual visit, examination should include those procedures that were done at the initial visit as outlined above or per recommendations of the Canadian Task Force on the Periodic Health Examination. **2. Pregnancy** Oral contraceptives should not be taken by pregnant women. However, if conception accidently occurs while taking the pill, there is no conclusive evidence that the estrogen and progestin contained in the oral contraceptive will damage the developing child. **3. Breastfeeding** In breastfeeding women, the use of oral contraceptives results in the hormonal components being excreted in breast milk and may reduce its quantity and quality. If the use of oral contraceptives is initiated after the establishment of lactation, there does not appear to be any effect on the quantity and quality of the milk. There is no evidence that low dose OCs are harmful to the nursing infant. **4. Hepatic Function** Patients who have had jaundice including a history of cholestatic jaundice during pregnancy should be given oral contraceptives with great care and under close observation. The development of severe generalized pruritus or icterus requires that the medication be withdrawn until the problem is resolved. If a patient develops jaundice which proves to be cholestatic in type, the use of oral contraceptives should not be resumed. In patients taking oral contraceptives, changes in the composition of the bile may occur and an increased incidence of gallstones has been reported. Hepatic nodules (adenoma and focal nodular hyperplasia) have been reported, particularly in long-term users of oral contraceptives. Although these lesions are extremely rare, they have caused fatal intra-abdominal hemorrhage and should be considered in women presenting with an abdominal mass, acute abdominal pain, or evidence of intra-abdominal bleeding. **5. Hypertension** Patients with essential hypertension whose blood pressure is well-controlled may be given oral contraceptives but only under close supervision. If a significant elevation of blood pressure in previously normotensive or hypertensive subjects occurs at any time during the administration of the drug, cessation of medication is necessary. **6. Migraine and Headache** The onset or exacerbation of migraine or the development of headache of a new pattern which is recurrent, persistent, or severe, requires discontinuation of oral contraceptives and evaluation of the cause. **7. Diabetes** Current low dose OCs exert minimal impact on glucose metabolism. Diabetic patients, or those with a family history of diabetes, should be observed closely to detect any worsening of carbohydrate metabolism. Patients predisposed to diabetes who can be kept under close supervision may be given oral contraceptives. Young diabetic patients whose disease is of recent origin, well-controlled, and not associated with hypertension or other signs of vascular disease such as ocular fundal changes, should be monitored more frequently while using oral contraceptives. **8. Ocular Disease** Patients who are pregnant or are taking oral contraceptives, may experience corneal edema that may cause visual disturbances and changes in tolerance to contact lenses, especially of the rigid type. Soft contact lenses usually do not cause disturbances. If visual changes or alterations in tolerance to contact lenses occur, temporary or permanent cessation of wear may be advised. **9. Breasts** Increasing age and a strong family history are the most significant risk factors for the development of breast cancer. Other established risk factors include obesity, nulliparity and late age at first full-term pregnancy. The identified groups of women that may be at increased risk of developing breast cancer before menopause are long-term users of oral contraceptives (more than 8 years) and starters at early age. In a few women, the use of oral contraceptives may accelerate the growth of an existing but undiagnosed breast cancer. Since any potential increased risk related to oral contraceptive use is small, there is no reason to change prescribing habits at present. Women receiving oral contraceptives should be instructed in self-examination of their breasts. Their physicians should be notified whenever any masses are detected. A yearly clinical breast examination is also recommended because, if a breast cancer should develop, estrogen-containing drugs may cause a rapid progression. **10. Vaginal Bleeding** Persistent irregular vaginal bleeding requires assessment to exclude underlying pathology. **11. Fibroids** Patients with fibroids (leiomyomata) should be carefully observed. Sudden enlargement, pain, or tenderness require discontinuation of the use of OCs. **12. Emotional Disorders** Patients with a history of emotional disturbances, especially the depressive type, may be more prone to have a recurrence of depression while taking oral contraceptives. In cases of a serious recurrence, a trial of an alternate method of contraception should be made which may help to clarify the possible relationship. Women with premenstrual syndrome (PMS) may have a varied response to oral contraceptives, ranging from symptomatic improvement to worsening of the condition. **13. Laboratory Tests** Results of laboratory tests should be interpreted in the light that the patient is on OCs. The following laboratory tests are modified. **A. Liver function tests** Aspartate serum transaminase (AST) – variously reported elevations. Alkaline phosphatase and gamma glutamine transaminase (GGT) – slightly elevated. **B. Coagulation tests** Minimal elevation of test values reported for such parameters as Factors VII, VIII, IX and X. **C. Thyroid function tests** Protein binding of thyroxine is increased as indicated by increased total serum thyroxine concentrations and decreased T_3 resin uptake. **D. Lipoproteins** Small changes of unproven clinical significance may occur in lipoprotein cholesterol fractions. **E. Gonadotropins** LH and FSH levels are suppressed by the use of oral contraceptives. Wait two weeks after discontinuing the use of oral contraceptives before measurements are made. **14. Tissue Specimens** Pathologists should be advised of oral contraceptive therapy when specimens obtained from surgical procedures and Pap smears are submitted for examination. **15. Return to Fertility** After discontinuing oral contraceptive therapy, the patient should delay pregnancy until at least one normal spontaneous cycle has occurred in order to date the pregnancy. An alternate contraceptive method should be used during this time. **16. Amenorrhea** Women having a history of oligomenorrhea, secondary amenorrhea, or irregular cycles may remain anovulatory or become amenorrheic following discontinuation of estrogen-progestin combination therapy. Amenorrhea, especially if associated with breast secretion, that continues for 6 months or more after withdrawal, warrants a careful assessment of hypothalamic-pituitary function. **17. Thromboembolic Complications – Post-surgery** There is an increased risk of post-surgery thromboembolic complications in oral contraceptive users, after major surgery. If feasible, oral contraceptives should be discontinued and an alternative method substituted at least one month prior to MAJOR elective surgery. Oral contraceptives should not be resumed until the first menstrual period after hospital discharge following surgery. **18. Drug Interactions** The concurrent administration of oral contraceptives with other drugs may result in an altered response to either agent. Reduced effectiveness of the oral contraceptive, should it occur, is more likely with the low dose formulations. It is important to ascertain all drugs that a patient is taking, both prescription and non-prescription, before oral contraceptives are prescribed.

TABLE I
Drugs Which May Decrease The Efficacy of Oral Contraceptives:

Anti-convulsants: *Carbamazepine, Ethosuximide, Phenobarbital, Phenytoin* and *Primidone*: Induction of hepatic microsomal enzymes: Rapid metabolism of estrogen and increased binding of progestin and ethinyl estradiol to SHBG. Use higher dose OCs (50 mcg ethinyl estradiol), another drug or another method. **Antibiotics:** *Ampicillin, Cotrimoxazole* and *Penicillin*: Enterohepatic circulation disturbance, intestinal hurry. For short course, use additional method or use another drug. For long course, use another method. *Rifampicin*: Increased metabolism of progestins. Suspected acceleration of estrogen metabolism. Use another method. *Chloramphenicol, Metronidazole, Neomycin, Nitrofurantoin, Sulfonamides* and *Tetracyclines*: Induction of hepatic microsomal enzymes. Also disturbance of enterohepatic circulation. For short course, use additional method or use another drug. For long course, use another method. *Troleandomycin*: May retard metabolism of OCs, increasing the risk of cholestatic jaundice. **Antifungal:** *Griseofulvin*: Stimulation of hepatic metabolism of contraceptive steroids may occur. Use another method. **Sedatives and Hypnotics:** *Benzodiazepines, Barbiturates, Chloral hydrate, Glutethimide* and *Meprobamate*: Induction of hepatic microsomal enzymes. For short course, use additional method or another drug. For long course use another method or higher dose OCs. **Antacids:** Decreased intestinal absorption of progestins. **Other Drugs:** *Phenylbutazone, Antihistamines, Analgesics, Antimigraine preparations, Vitamin E*: Reduced OC efficacy has been reported. Remains to be confirmed.

TABLE II
Modification of Other Drug Action by Oral Contraceptives:

Alcohol: Possible increased levels of ethanol or acetaldehyde. Use with caution. **Alpha-II Adrenoreceptor Agents:** *Clonidine*: Sedation effect increased. Use with caution. **Anti-coagulants:** *All*: OCs increase clotting factors, decrease efficacy. However, OC may potentiate action in some patients. Use another method. **Anti-convulsants:** *All*: Fluid retention may increase risk of seizures. Use another method. **Anti-diabetic Drugs:** *Oral hypoglycemics* and *Insulin*: OCs may impair glucose tolerance and increase blood glucose. Use low dose estrogen and progestin OC or another method. Monitor blood glucose. **Anti-hypertensive Agents:** *Guanethidine* and *Methyldopa*: Estrogen component causes sodium retention, progestin has no effect. Use low estrogen OC or use another method. *Beta blockers*: Increased drug effect (decreased metabolism). Adjust dose of drug if necessary. Monitor cardiovascular status. **Antipyretics:** *Acetaminophen*: Increased renal clearance. Dose of drug may have to be increased. *Antipyridine*: Impaired metabolism. Decrease dose of drug. *ASA*: Effects of ASA may be decreased by the short-term use of OCs. Patients on chronic ASA therapy may require an increase in ASA dosage. **Aminocaproic Acid:** Theoretically, a hypercoagulable state may occur because OCs augment clotting factors. Avoid concomitant use. **Betamimetic Agents:** *Isoproterenol*: Estrogen causes decreased response to these drugs. Adjust dose of drug as necessary. Discontinuing OCs can result in excessive drug activity. **Caffeine:** The actions of caffeine may be enhanced as OCs may impair the hepatic metabolism of caffeine. Use with caution. **Cholesterol Lowering Agents:** *Clofibrate*: OC may increase the clearance of clofibrate leading to decreased levels of clofibrate. Use with caution. **Corticosteroids**: *Prednisone*: Markedly increased serum levels. Possible need for decrease in dose. **Cyclosporine:** May lead to an increase in cyclosporine levels and hepatotoxicity. Monitor hepatic function. The cyclosporine dose may have to be decreased. **Folic Acid:** OCs have been reported to impair folate metabolism. **Meperidine:** Possible increased analgesia and CNS depression due to decreased metabolism of meperidine. Use combination with caution. **Phenothiazine Tranquilizers:** *All Phenothiazines, Reserpine and Similar Drugs*. Estrogen potentiates the hyperprolactinemia effect of these drugs. Use other drugs or lower dose OCs. If galactorrhea or hyperprolactinemia occurs use other method. **Sedatives and Hypnotics:** *Chlordiazepoxide, Lorazepam, Oxazepam* and *Diazepam*: Increased effect (increased metabolism). Use with caution. **Theophylline:** *All*: Decreased oxidation, leading to possible toxicity. Use with caution. Monitor theophylline levels. **Tricyclic Anti-depressants:** *Clomipramine (possibly others)*: Increased side effects: i.e. depression. Use with caution. **Vitamin B_{12}:** OCs have been reported to reduce serum levels of Vitamin B_{12}.

ADVERSE REACTIONS

An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives: Thrombophlebitis, Pulmonary embolism, Mesenteric thrombosis, Neuro-ocular lesions e.g. retinal thrombosis, Myocardial infarction, Cerebral thrombosis, Cerebral hemorrhage, Hypertension, Benign hepatic tumours, Gallbladder disease.

The following adverse reactions also have been reported in patients receiving oral contraceptives: Nausea and vomiting, usually the most common adverse reaction, occurs in approximately 10% or less of patients during the first cycle. Other reactions, as a general rule, are seen less frequently or only occasionally.

Other Adverse Reactions: Gastrointestinal symptoms (such as abdominal cramps and bloating). Change in menstrual flow: Temporary infertility after discontinuation of treatment. Edema. Melasma which may persist. Breast changes: tenderness, enlargement, secretion. Change in weight (increase or decrease). Change in cervical erosion and secretion. Cholestatic jaundice. Rash (allergic). Vaginal candidiasis. Change in corneal curvature (steepening).

The following adverse reactions have been reported in users of oral contraceptives, and the association has been neither confirmed nor refuted: Congenital anomalies. Premenstrual syndrome. Cataracts. Optic neuritis. Changes in appetite. Cystitis-like syndrome. Headache. Nervousness. Dizziness. Hirsutism. Loss of scalp hair. Erythema multiforme. Erythema nodosum. Hemorrhagic eruption. Vaginitis. Porphyria. Impaired renal syndrome. Hemolytic uremic syndrome. Budd-Chiari syndrome. Acne. Changes in libido. Colitis. Sickle-cell disease. Cerebral-vascular disease with mitral valve prolapse. Lupus-like syndrome.

DOSAGE AND ADMINISTRATION: TRIPHASIL® 21 TABLETS REGIMEN

Each cycle consists of 21 days on medication and a 7-day interval without medication (three weeks on, one week off).The 21-day regimen is comprised of the first six days of pale brown tablets, followed by five days of white tablets, followed by ten days of yellow tablets. For the first cycle of medication, the patient is instructed to take one Triphasil® Tablet daily for 21 consecutive days beginning on Day 1 of her menstrual cycle, on Day 5, or on the first Sunday after her period begins. (For the first cycle only, the first day of menstrual flow is considered Day 1.) The tablets are then discontinued for seven days (one week). Withdrawal bleeding should usually occur during the period that the patient is off the tablets. The patient begins her next and all subsequent 21-day courses of Triphasil® Tablets (following the same 21 days on, 7 days off) on the same day of the week that she began her first course. She begins taking her tablets seven days after discontinuation, regardless of whether or not withdrawal bleeding is still in progress.

TRIPHASIL® 28 TABLETS REGIMEN

Each cycle consists of 21 days of Triphasil® Tablets followed by 7 days of inert tablets (three weeks on Triphasil®, one week on inert tablets). The 28-day regimen is comprised of the first six days of pale brown tablets, followed by five days of white tablets, followed by ten days of yellow tablets, followed by seven days of inert green tablets. For the first cycle of medication, the patient is instructed to take one tablet for 28 consecutive days beginning on Day 1 of her menstrual cycle, on Day 5, or on the first Sunday after her period begins. (For the first cycle only, the first day of menstrual flow is considered Day 1.) Withdrawal bleeding should usually occur during the week the patient is taking the inert green tablets. The patient begins her next and all subsequent 28-day courses of tablets on the same day of the week that she began her first course. She continues her next course of 28 tablets immediately after the last course regardless of whether or not a period of withdrawal bleeding is still in progress. There is no need for the patient to count days between cycles because there are no "off-tablet days."

SPECIAL NOTES ON ADMINISTRATION

It is recommended that Triphasil® Tablets be taken at the same time each day, preferably after the evening meal or at bedtime. Triphasil® is effective from the first day of therapy if the tablets are begun as described under "DOSAGE AND ADMINISTRATION." If Triphasil® Tablets administration is initiated later than the fifth day of the first menstrual cycle of medication or postpartum, contraceptive reliance should not be placed on Triphasil® until after the first seven consecutive days of administration. The possibility of ovulation and conception prior to initiation of medication should be considered. In the non-lactating mother, Triphasil® may be prescribed in the postpartum period either immediately or at the first postpartum examination, whether or not menstruation has resumed. If spotting or breakthrough bleeding occurs, the patient is instructed to continue on the same regimen. This type of bleeding usually is transient and without significance; however, if the bleeding is persistent or prolonged, the patient is advised to consult her physician. The patient should be instructed to use the following chart if she misses one or more of her birth control pills. She should be told to match the number of pills with the appropriate starting time for her type of pill.

SUNDAY START

Miss 1 Pill: Take it as soon as you remember, and take the next pill at the usual time. This means that you might take 2 pills in one day. **Miss 2 Pills in a Row: First 2 Weeks:** 1. Take 2 pills the day you remember and 2 pills the next day. 2. Then take 1 pill a day until you finish the pack. 3. Use a back-up method of birth control if you have sex in the 7 days after you miss the pills. **Third Week** 1. Keep taking 1 pill a day until Sunday. 2. On Sunday, safely discard the rest of the pack and start a new pack that day. 3. Use a back up method of birth control if you have sex in the 7 days after you miss the pills. 4. You may not have a period this month. **If You Miss 2 Periods in a Row, Call Your Doctor or Clinic. Miss 3 or More Pills in a Row: Any Time in the Cycle:** 1. Keep taking 1 pill a day until Sunday. 2. On Sunday, safely discard the rest of the pack and start a new pack that day. 3. Use a back-up method of birth control if you have sex in the 7 days after you miss the pills. 4. You may not have a period this month. **If You Miss 2 Periods in a Row, Call Your Doctor or Clinic.**

OTHER THAN SUNDAY START

Miss 1 Pill: Take it as soon as you remember, and take the next pill at the usual time. This means that you might take 2 pills in one day. **Miss 2 Pills in a Row: First 2 Weeks:** 1. Take 2 pills the day you remember and 2 pills the next day. 2. Then take 1 pill a day until you finish the pack. 3. Use a back-up method of birth control if you have sex in the 7 days after you miss the pills. **Third Week** 1. Safely dispose of the rest of the pill pack and start a new pack that same day. 2. Use a back-up method of birth control if you have sex in the 7 days after you miss the pills. 3. You may not have a period this month. **If You Miss 2 Periods in a Row, Call Your Doctor or Clinic. Miss 3 or More Pills in a Row: Any Time in the Cycle:** 1. Safely dispose of the rest of the pill pack and start a new pack that same day. 2. Use a back-up method of birth control if you have sex in the 7 days after you miss the pills. 3. You may not have a period this month. **If You Miss 2 Periods in a Row, Call Your Doctor or Clinic.**

AVAILABILITY OF DOSAGE FORMS

TRIPHASIL® Tablets are available in 21-day and 28-day Tablet Dispenser units. Each pale brown tablet contains 50 µg levonorgestrel plus 30 µg ethinyl estradiol. Each white tablet contains 75 µg levonorgestrel plus 40 µg ethinyl estradiol. Each yellow tablet contains 125 µg levonorgestrel plus 30 µg ethinyl estradiol. In the 28-day regimen, each green tablet contains inert ingredients.

REFERENCES

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WYETH-AYERST CANADA INC.
Montreal, Canada H4R 1J6

Product monograph available upon request.

PAAB

Imdur®

ONCE-A-DAY

EXTENDED RELEASE ISOSORBIDE-5-MONONITRATE

NAME OF DRUG: IMDUR (Isosorbide-5-mononitrate (5-ISMN)) 60 mg extended release tablets.

THERAPEUTIC CLASSIFICATION: Antianginal agent.

ACTIONS AND CLINICAL PHARMACOLOGY: As with other organic nitrates, the principal pharmacological action of IMDUR (5-ISMN), the major active metabolite of isosorbide dinitrate (ISDN), is relaxation of vascular smooth muscle and consequent dilation of peripheral arteries and veins, especially the latter. Dilation of the veins promotes peripheral pooling of blood and decreases venous return to the heart, thereby reducing left ventricular end-diastolic pressure and pulmonary capillary wedge pressure (pre-load). Arteriolar relaxation reduces systemic vascular resistance, systolic arterial pressure, and mean arterial pressure (after-load). Dilation of the coronary arteries also occurs. The hemodynamic responses to 5-ISMN are similar to those produced by other nitrates.

Pharmacodynamics Dosage regimens for most chronically used drugs are designed to provide plasma concentrations that are continuously greater than a minimally effective concentration. This strategy is inappropriate for organic nitrates. Prolonged administration of nitrate drugs according to traditionally recommended dosage regimens has been shown to produce tolerance. Tolerance results in a loss of efficacy. Several well-controlled clinical trials have used exercise testing to assess the antianginal efficacy of continuously delivered nitrates. In the large majority of these trials, nitrate effectiveness was indistinguishable from placebo after 24 hours (or less) of continuous therapy. Attempts to overcome tolerance by dose escalation, even to doses far in excess of those used acutely, have consistently failed. Only after nitrates have been absent from the body for several hours has their antianginal efficacy been restored. Drug-free intervals of 10 to 12 hours are known to be sufficient to restore response. The drug-free interval sufficient to avoid tolerance to 5-ISMN has not been completely defined. IMDUR tablets during long-term use over 42 days dosed at 120 mg once daily continued to improve exercise performance at 4 hours and 12 hours after dosing but its effects (although better than placebo) are less than or at best equal to the effects of the first dose of 60 mg. Considering the pharmacokinetic profile of 5-ISMN and its long half-life (see Pharmacokinetics), clinical efficacy is consistent with that observed for other organic nitrates.

Pharmacokinetics After oral administration of 5-ISMN as a solution or immediate-release tablets, maximum plasma concentrations of 5-ISMN are achieved in 30 to 60 minutes with an absolute bioavailability of approximately 100%. After intravenous administration, 5-ISMN is distributed into total body water in about 9 minutes with a volume of distribution of approximately 0.6-0.7 L/kg. 5-ISMN is approximately 5% bound to human plasma proteins and is distributed into blood cells and saliva. 5-ISMN is primarily metabolized by the liver, but unlike oral isosorbide dinitrate, it is not subject to first-pass metabolism. 5-ISMN is cleared by denitration to isosorbide and glucuronidation as the mononitrate, with 96% of the administered dose excreted in the urine within 5 days and only about 1% eliminated in the feces. At least 6 different compounds have been detected in urine, with about 2% of the dose excreted as the unchanged drug and at least 5 metabolites. The metabolites are not pharmacologically active. Renal clearance accounts for only about 4% of total body clearance. The mean plasma elimination half life of 5-ISMN is approximately 5 hours. The disposition of 5-ISMN in patients with various degrees of renal insufficiency, liver cirrhosis or cardiac dysfunction was evaluated and found to be similar to that observed in healthy subjects. The elimination half-life of 5-ISMN was not prolonged, and there was no drug accumulation in patients with chronic renal failure after multiple oral dosing. Impaired liver or kidney function has no major influence on the pharmacokinetic properties. Food intake may decrease the rate (increase in T_{max}) but not the extent (AUC) of absorption of 5-ISMN. With the extended release formulation of IMDUR, 5-ISMN is gradually released, independent of pH, over a 10-hour period, according to a first order process. This prolongation of the absorption phase results in reduced and delayed peak plasma levels compared to conventional tablets of 5-ISMN. After administration of 60 mg of 5-ISMN extended release tablets, peak plasma levels of around 3000 nmol/L are usually obtained within approximately 4 hours. The plasma concentrations then gradually fall to around 500 nmol/L at the end of the dosage interval (24 hours after dose intake).

INDICATIONS AND CLINICAL USE: IMDUR (5-ISMN) is indicated for the prevention of anginal attacks in patients with chronic stable angina pectoris associated with coronary artery disease. IMDUR is not intended for the immediate relief of acute attacks of angina pectoris.

CONTRAINDICATIONS: • Known hypersensitivity to 5-ISMN or to other nitrates or nitrites. • Acute circulatory failure associated with marked hypotension (shock and states of collapse). • Postural hypotension. • Myocardial insufficiency due to obstruction (e.g. in the presence of aortic or mitral stenosis or of constrictive pericarditis). • Increased intracranial pressure. • Severe anemia.

WARNINGS: The benefits and safety of IMDUR (5-ISMN) in anginal patients with acute myocardial infarction or congestive heart failure have not been established. Because the effects of 5-ISMN are difficult to terminate rapidly, this drug is not recommended in these settings. Abrupt withdrawal may occasionally aggravate anginal symptoms. To avoid possible withdrawal effects, the administration of IMDUR (5-ISMN) should be gradually reduced and not abruptly discontinued. Caution should be observed in patients with severe cerebral arteriosclerosis or severe hypotension.

PRECAUTIONS: Headaches or symptoms of severe hypotension, such as weakness or dizziness, particularly when arising suddenly from a recumbent position, may occur. Caution should be exercised when using nitrates in patients prone to, or who might be affected by, hypotension. IMDUR (5-ISMN) should therefore be used with caution in patients who may have volume depletion from diuretic therapy or in patients who have low systolic blood pressure (e.g. ≤ 90 mmHg). Paradoxical bradycardia and increased angina pectoris may accompany nitrate-induced hypotension. Nitrate therapy may aggravate the angina caused by hypertrophic cardiomyopathy. In industrial workers who have had long-term exposure to unknown (presumably high) doses of organic nitrates, tolerance clearly occurs. There is, moreover, physical dependence since chest pain, acute myocardial infarction, and even sudden death have occurred during temporary withdrawal of nitrates from these workers. In clinical trials of angina patients, there are reports of anginal attacks being more easily provoked and of rebound in the hemodynamic effects soon after nitrate withdrawal. The importance of these observations to the routine, clinical use of oral 5-ISMN has not been fully elucidated. Caution should be exercised in patients with arterial hypoxemia due to anemia (see CONTRAINDICATIONS). Similarly, caution is called for in patients with hypoxemia and a ventilation/perfusion imbalance due to lung disease or ischemic heart failure. Patients with angina pectoris, myocardial infarction or cerebral ischemia frequently suffer from abnormalities of the small airways (especially alveolar hypoxia). Under these circumstances vasoconstriction occurs within the lung to shift perfusion from areas of alveolar hypoxia to better ventilated regions of the lung. As a potent vasodilator, 5-ISMN could reverse this protective vasoconstriction and thus result in increased perfusion to poorly ventilated areas, worsening of the ventilation/perfusion imbalance, and a further decrease in the arterial partial pressure of oxygen. Tolerance to 5-ISMN with cross tolerance to other nitrates or nitrites may occur (see ACTIONS AND CLINICAL PHARMACOLOGY). As tolerance to 5-ISMN develops, the effect of sublingual nitroglycerin on exercise tolerance, although still observable, is somewhat blunted. As patients may experience faintness and/or dizziness, reaction time when driving or operating machinery may be impaired, especially at the start of treatment.

Use in Pregnancy Teratogenic effects: In studies designed to detect effects of 5-ISMN on embryo-fetal development, doses of up to 240 or 248 mg/kg/day, administered to pregnant rats and rabbits, were unassociated with evidence of such effects. No adverse effects on reproduction or fetal development were reported. These animal doses are about 100 times the maximum recommended human dose when comparison is based on body weight; when comparison is based on body surface area, the rat dose is about 17 times the human dose and the rabbit dose is about 38 times the human dose. There are no studies in pregnant women. Because animal reproduction studies are not always predictive of human response, IMDUR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Non-teratogenic Effects: Neonatal survival and development and incidence of stillbirths were adversely affected when pregnant rats were administered oral doses of 750 (but not 300) mg 5-ISMN/kg/day during late gestation and lactation. This dose (about 312 times the human dose when comparison is based on body weight and 54 times the human dose when comparison is based on body surface area) was associated with decreases in maternal weight gain and motor activity and evidence of impaired lactation.

Use in Nursing Mothers It is not known whether 5-ISMN is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when 5-ISMN is administered to a nursing mother.

Use in Children The safety and efficacy of 5-ISMN in children have not been established. Therefore, its use is not recommended.

Drug Interactions Concomitant treatment with other vasodilators, calcium antagonists, ACE inhibitors, beta-blockers, diuretics, antihypertensives, tricyclic antidepressants, and major tranquilizers may potentiate the blood pressure lowering effect of IMDUR. Marked symptomatic orthostatic hypotension has been reported when calcium channel blockers and organic nitrates were used in combination. Dose adjustments of either class of agents may be necessary. Alcohol may enhance sensitivity to the hypotensive effects of nitrates.

ADVERSE REACTIONS: In 17 clinical trials, both controlled and uncontrolled, 861 patients were treated with IMDUR (5-ISMN) 30 mg to 240 mg once daily, alone or in combination with ß-adrenergic blocking agents. Adverse events were reported in 71% of the patients. Discontinuation of therapy due to adverse reactions was required in 8% of the patients. Most of these were discontinued because of headache. Dizziness, myocardial infarction, nausea, and vertigo were also associated with withdrawal from these studies. The most common adverse events were headache, dizziness, fatigue, nausea and flushing. The following adverse events were reported by >1-3% of patients: myocardial infarction, postural hypotension, tachycardia, angina pectoris, somnolence, coughing, paresthesia, vertigo, abdominal pain, diarrhea, flatulence, extra systoles, palpitation, aggravated angina, insomnia, dyspnea, respiratory infection, increased sweating, vasospasm, abnormal vision, back pain, musculoskeletal pain, dyspepsia, chest pain, rhinitis, constipation. The following adverse events were reported in ≤1% of the patients:

Cardiovascular: bundle branch block, cardiac failure, circulatory failure, hypotension, hypertension, syncope, arrhythmia, AV block, bradycardia, atrial fibrillation, heart murmur, abnormal heart sound, Q-wave abnormality, T-wave changes, ECG abnormal.

Dermatological: rash, pruritus, eczema, acne, rash erythematous, rash psoriaform, abnormal hair texture, skin disorder.

Gastrointestinal: duodenal ulcer, eructation, hemorrhagic gastric ulcer, gastritis, hemorrhoids, intestinal obstruction, melena, dry mouth, pharynx disorder, tooth disorder, vomiting, loose stools, glossitis.

Genitourinary: atrophic vaginitis, prostatic disorder, renal calculus, urinary bladder diverticulum, urinary tract infection, polyuria.

Miscellaneous: allergic reaction, asthenia, female breast pain, edema, feeling of warmth, fever, flu-like symptoms, malaise, rigors, earache, biliary pain, cholecystitis, hepatomegaly, diabetes mellitus, gout, weight decrease, weight increase, peripheral edema, tinnitus, epistaxis, purpura, infection, bacterial infection, cerebrovascular disorder, intermittent claudication, leg ulcer, peripheral ischemia, varicose vein, amaurosis fugax, conjunctivitis, diplopia, photophobia, moniliasis, skin nodule, tympanic membrane perforation, allergy, pain.

Musculoskeletal: arthralgia, arthritis, arthropathy, arthrosis, frozen shoulder, muscle weakness, myalgia, myositis, torticollis, tendon disorder.

Neurological: hypoesthesia, migraine, neuritis, tremor, agitation, amnesia, impaired concentration, depression, decreased libido, nervousness, paroniria, confusion, anxiety, paresis, ptosis, impotence.

Respiratory: bronchitis, bronchospasm, pharyngitis, pneumonia, rales, respiratory disorder, pulmonary infiltration, increased sputum, sinusitis, nasal congestion.

Laboratory Changes: albuminuria, hematuria, gamma GT increased, SGOT increased, SGPT increased, hypercholesterolemia, hyperlipemia, hyperuricemia, hypocalcemia, hypokalemia, increased non-protein nitrogen, thrombocytopenia, anemia, leucopenia, leukocytosis, glycosuria.

SYMPTOMS AND TREATMENT OF OVERDOSAGE: **Hemodynamic Effects** Symptoms of IMDUR (5-ISMN) overdose are generally the results of vasodilation, venous pooling, reduced cardiac output, and hypotension. These hemodynamic changes may have protean manifestations, including increased intracranial pressure, with any or all of persistent throbbing headache, confusion, and moderate fever; vertigo; palpitations; visual disturbances; nausea and vomiting (possibly with colic and even bloody diarrhea); syncope (especially in the upright posture); air hunger and dyspnea, later followed by reduced ventilatory effort; diaphoresis, with the skin either flushed or cold and clammy; heart block and bradycardia; paralysis; coma; seizures and death. No specific antagonist to the vasodilator effects of 5-ISMN is known, and no intervention has been subject to controlled study as a therapy of 5-ISMN overdose. Because the hypotension associated with 5-ISMN overdose is the result of venodilation and arterial hypovolemia, prudent therapy in this situation should be directed toward an increase in central fluid volume. Passive elevation of the patient's legs may be sufficient, but intravenous infusion of normal saline or similar fluid may also be necessary. In patients with renal disease or congestive heart failure, therapy resulting in central volume expansion is not without hazard. Treatment of 5-ISMN overdose in these patients may be subtle and difficult, and invasive monitoring may be required. The use of epinephrine or other vasoconstrictors is ineffective in reversing the severe hypotensive effects of overdose and is therefore contraindicated in this situation. Dialysis is known to be ineffective in removing 5-ISMN from the body.

Methemoglobinemia Methemoglobinemia has been reported in patients receiving other organic nitrates, and it may occur as a side effect of 5-ISMN. Nitrate ions liberated during metabolism of 5-ISMN can oxidize hemoglobin into methemoglobin. In patients totally without cytochrome b_5 reductase activity, about 2 mg/kg of 5-ISMN would be required before any of these patients manifests clinically significant (≥10%) methemoglobinemia. In patients with normal reductase function, significant production of methemoglobin would require even larger doses of 5-ISMN. Methemoglobin levels are available from most clinical laboratories. The diagnosis should be suspected in patients who exhibit signs of impaired oxygen delivery despite adequate cardiac output and adequate arterial pO_2. Classically, methemoglobinemic blood is described as chocolate brown without colour change on exposure to air. When methemoglobinemia is diagnosed, administration of methylene blue, 1-2 mg/kg intravenously, may be required.

DOSAGE AND ADMINISTRATION: IMDUR (5-ISMN), administered once daily, provides efficacy for up to 12 hours. This formulation is designed to avoid or attenuate the development of tolerance. The recommended starting dose of IMDUR, for those patients who are active during the day, is 60 mg (one tablet) once daily to be taken in the morning on arising. The dose may be increased to 120 mg (two tablets) once daily. Rarely 240 mg may be required. To minimize the possibility of headache the dose can be titrated by initiating treatment with 30 mg (half a tablet) for the first 2-4 days. Dosage adjustments are not necessary for elderly patients or patients with altered renal or hepatic function. The tablet may be taken whole or as divided halves. The tablets should not be chewed or crushed, and should be swallowed together with half a glass of water. NOTE: IMDUR is not indicated for the relief of acute anginal attacks; in these situations sublingual or buccal nitroglycerin should be used.

Full product monograph available on request.

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ASTRA

Astra Pharma Inc., Mississauga, Ontario L4Y 1M4

℞FOSAMAX®

alendronate tablets

10 mg and 40 mg

(as alendronate sodium)

Bone Metabolism Regulator

ACTIONS AND CLINICAL PHARMACOLOGY

FOSAMAX® (alendronate sodium) is an aminobisphosphonate that acts as a potent, specific inhibitor of osteoclast-mediated bone resorption. Bisphosphonates are synthetic analogs of pyrophosphate that bind to the hydroxyapatite found in bone.

Pharmacokinetics

Absorption

Relative to an intravenous (IV) reference dose, the mean oral bioavailability of alendronate in women was 0.7% for doses ranging from 5 to 40 mg when administered after an overnight fast and two hours before a standardized breakfast. Oral bioavailability of the 10 mg tablet in men (0.59%) was similar to that in women (0.78%) when administered after an overnight fast and 2 hours before breakfast.

A study examining the effect of timing of a meal on the bioavailability of alendronate was performed in 49 postmenopausal women. Bioavailability was decreased (by approximately 40%) when 10 mg alendronate was administered either 0.5 or 1 hour before a standardized breakfast, when compared to dosing 2 hours before eating. Bioavailability was negligible whether alendronate was administered with or up to two hours after a standardized breakfast. Concomitant administration of alendronate with coffee or orange juice reduced bioavailability by approximately 60%.

In a trial in elderly patients given 5 mg of alendronate (n = 86) 30 minutes before breakfast, similar bone mineral density changes were noted when compared to the pivotal trials, in which one of the treatment arms was 5 mg alendronate administered 60 minutes before breakfast.

Distribution

Preclinical studies (in male rats) show that alendronate transiently distributes to soft tissues following 1 mg/kg IV administration but is then rapidly redistributed to bone or excreted in the urine. The mean steady-state volume of distribution, exclusive of bone, is at least 28 L in humans. Concentrations of drug in plasma following therapeutic oral doses are too low (less than 5 mg/mL) for analytical detection. Protein binding in human plasma is approximately 78%.

Metabolism

There is no evidence that alendronate is metabolized in animals or humans.

Excretion

Following a single IV dose of [^{14}C]alendronate, approximately 50% of the radioactivity was excreted in the urine within 72 hours and little or no radioactivity was recovered in the feces. Following a single 10 mg IV dose, the renal clearance of alendronate was 71 mL/min, and systemic clearance did not exceed 200 mL/min. Plasma concentrations fell by more than 95% within 6 hours following IV administration. The terminal half-life in humans is estimated to exceed 10 years, probably reflecting release of alendronate from the skeleton. Based on the above, it is estimated that after 10 years of oral treatment with FOSAMAX® (10 mg daily) the amount of alendronate released daily from the skeleton is approximately 25% of that absorbed from the gastrointestinal tract.

Special Populations

Pediatric

Alendronate pharmacokinetics have not been investigated in patients < 18 years of age.

Gender

Bioavailability and the fraction of an IV dose excreted in urine were similar in men and women.

Geriatric

Bioavailability and disposition (urinary excretion) were similar in elderly (≥ 65 years of age) and younger patients. No dosage adjustment is necessary (see DOSAGE AND ADMINISTRATION).

Race

Pharmacokinetic differences due to race have not been studied.

Renal Insufficiency

Preclinical studies show that, in rats with kidney failure, increasing amounts of drug are present in plasma, kidney, spleen, and tibia. In healthy controls, drug that is not deposited in bone is rapidly excreted in the urine. No evidence of saturation of bone uptake was found after 3 weeks dosing with cumulative IV doses of 35 mg/kg in young male rats. Although no clinical information is available, it is likely that, as in animals, elimination of alendronate via the kidney will be reduced in patients with impaired renal function. Therefore, somewhat greater accumulation of alendronate in bone might be expected in patients with impaired renal function.

No dosage adjustment is necessary for patients with mild-to-moderate renal insufficiency (creatinine clearance 35 to 60 mL/min). FOSAMAX® is not recommended for patients with more severe renal insufficiency (creatinine clearance < 35 mL/min) due to lack of experience.

Hepatic Insufficiency

As there is evidence that alendronate is not metabolized or excreted in the bile, no studies were conducted in patients with hepatic insufficiency. No dosage adjustment is necessary.

Drug Interactions (also see PRECAUTIONS, Drug Interactions)

Intravenous ranitidine was shown to double the bioavailability of oral alendronate. The clinical significance of this increased bioavailability and whether similar increases will occur in patients given oral H_2-antagonists is unknown; no other specific drug interaction studies were performed.

Products containing calcium and other multivalent cations likely will interfere with absorption of alendronate.

Summary of Pharmacokinetic Parameters in the Normal Population

	Mean	90% Confidence Interval
Absolute bioavailability of 10 mg tablet, taken 2 hours before first meal of the day	0.78% (females) 0.59% (males)	(0.61, 1.04) (0.43, 0.81)
Absolute bioavailability of 40 mg tablet, taken 2 hours before first meal of the day	0.60% (females)	(0.46, 0.78)
Renal Clearance (mL/min) (n = 6)	71	(64,78)

Pharmacodynamics

Osteoporosis in postmenopausal women

Osteoporosis is characterized by low bone mass that leads to an increased risk of fracture. The diagnosis can be confirmed by the finding of low bone mass, evidence of fracture on x-ray, a history of osteoporotic fracture, or height loss or kyphosis, indicative of vertebral fracture. Osteoporosis occurs in both males and females but is most common among women following the menopause, when bone turnover increases and the rate of bone resorption exceeds that of bone formation. These changes result in progressive bone loss and lead to osteoporosis in a significant proportion of women over age 50. Fractures, usually of the spine, hip, and wrist, are the common consequences. From age 50 to age 90, the risk of hip fracture in white women increases 50-fold and the risk of vertebral fracture 15- to 30-fold. It is estimated that approximately 40% of 50-year-old women will sustain one or more osteoporosis-related fractures of the spine, hip, or wrist during their remaining lifetimes. Hip fractures, in particular, are associated with substantial morbidity, disability, and mortality.

Alendronate is an aminobisphosphonate that binds to bone hydroxyapatite and specifically inhibits the activity of osteoclasts, the bone-resorbing cells. Alendronate reduces bone resorption with no direct effect on bone formation, although the latter process is ultimately reduced because bone resorption and formation are coupled during bone turnover. Alendronate thus reduces the elevated rate of bone turnover observed in postmenopausal women to approximate more closely that in premenopausal women.

Daily oral doses of alendronate (5, 20, and 40 mg for six weeks) in postmenopausal women produced biochemical changes indicative of dose-dependent inhibition of bone resorption, including decreases in urinary calcium and urinary markers of bone collagen degradation (such as deoxypyridinoline and cross-linked N-telopeptides of type I collagen). These biochemical changes tended to return toward baseline values as early as 3 weeks following the discontinuation of therapy with alendronate and did not differ from placebo after 7 months.

In long-term (two- or three-year) studies, FOSAMAX® 10 mg/day reduced urinary excretion of markers of bone resorption, including deoxypyridinoline and cross-linked N-telopeptides of type I collagen, by approximately 50-60% to reach levels similar to those seen in healthy premenopausal women. The decrease in the rate of bone resorption indicated by these markers was evident as early as one month and at three to six months reached a plateau that was maintained for the entire duration of treatment with FOSAMAX®. In addition, the markers of bone formation, serum osteocalcin and alkaline phosphatase, were also reduced by approximately 50% and 25 to 30%, respectively, to a plateau after 6 to 12 months. These data indicate that the rate of bone turnover reached a new steady-state, despite the progressive increase in the total amount of alendronate deposited within bone.

As a result of inhibition of bone resorption, asymptomatic reductions in serum calcium and phosphate concentrations were also observed following treatment with FOSAMAX®. In the long-term studies, reductions from baseline in serum calcium (approximately 2%) and phosphate (approximately 4 to 6%) were evident the first month after the initiation of FOSAMAX® 10 mg, but no further decreases were observed for the three-year duration of the studies. The reduction in serum phosphate may reflect not only the positive bone mineral balance due to FOSAMAX® but also a decrease in renal phosphate reabsorption.

Paget's disease

Paget's disease of bone is a chronic, focal skeletal disorder characterized by greatly increased and disorderly bone remodeling. Excessive osteoblastic bone resorption is followed by osteoblastic new bone formation, leading to the replacement of the normal bone architecture by disorganized, enlarged, and weakened bone structure.

Clinical manifestations of Paget's disease range from no symptoms to severe morbidity due to bone pain, bone deformity, pathological fractures, and neurological and other complications. Serum alkaline phosphatase, the most frequently used biochemical index of disease activity, provides an objective measure of disease severity and response to therapy.

FOSAMAX® decreases the rate of bone resorption directly, which leads to an indirect decrease in bone formation. In clinical trials, FOSAMAX® 40 mg once daily for six months produced highly significant decreases in serum alkaline phosphatase as well as in urinary markers of bone collagen degradation. As a result of the inhibition of bone resorption, FOSAMAX® induced generally mild, transient, and asymptomatic decreases in serum calcium and phosphate.

INDICATIONS AND CLINICAL USE

FOSAMAX® (alendronate sodium) is indicated for the treatment of:

- **Osteoporosis in postmenopausal women.**
  Osteoporosis may be confirmed by the finding of low bone mass (for example, at least 2.0 standard deviations below the premenopausal mean) or by the presence or history of osteoporotic fracture.
- **Paget's disease of bone.**
  Treatment is indicated in patients with Paget's disease of bone having serum alkaline phosphatase at least two times the upper limit of normal, or those who are symptomatic, or those at risk for future complications from their disease.

CONTRAINDICATIONS

- Hypersensitivity to any component of this product
- Hypocalcemia (see PRECAUTIONS)
- Renal insufficiency with creatinine clearance < 35 mL/min (see DOSAGE AND ADMINISTRATION)

PRECAUTIONS

As with other bisphosphonates, caution should be used when FOSAMAX® (alendronate sodium) is given to patients with active upper gastrointestinal problems, such as dysphagia, symptomatic esophageal diseases, gastritis, duodenitis, or ulcers. FOSAMAX® should be taken as directed with a full glass of water to ensure delivery to the stomach.

Causes of osteoporosis other than estrogen deficiency and aging should be considered.

Hypocalcemia must be corrected before initiating therapy with FOSAMAX® (see CONTRAINDICATIONS). Other disturbances of mineral metabolism (such as vitamin D deficiency) should be treated.

Paget's Disease

Due to the positive effects of FOSAMAX® to increase bone mineral, small, asymptomatic decreases in serum calcium and phosphate may occur, especially in patients with Paget's disease, in whom the pretreatment rate of bone turnover may be greatly elevated. Adequate calcium and vitamin D nutrition must be ensured to provide for these enhanced needs.

Use in the Elderly

In clinical studies, there was no age-related difference in the efficacy or safety profiles of FOSAMAX®.

Use in Children

FOSAMAX® has not been studied in patients < 18 years of age and should not be given to them.

Use in Obstetrics

FOSAMAX® has not been studied in pregnant women and should not be given to them.

Use in Nursing Mothers

FOSAMAX® has not been studied in nursing mothers and should not be given to them.

Use in Men

Safety and effectiveness in male osteoporosis have not been established.

Drug Interactions

It is likely that calcium supplements, antacids, and some oral medications will interfere with absorption of FOSAMAX®. Therefore, patients must wait at least one-half hour after taking FOSAMAX® before taking any other drug.

Intravenous ranitidine was shown to double the bioavailability of oral alendronate. The clinical significance of this increased bioavailability and whether similar increases will occur in patients given oral H_2-antagonists is unknown.

A small number of postmenopausal women in the osteoporosis trials received estrogen (intravaginal, transdermal, or oral) while taking FOSAMAX®. No adverse experiences attributable to their concomitant use were identified.

However, concomitant use of hormone replacement therapy and FOSAMAX® in the treatment of osteoporosis in postmenopausal women is not recommended due to the lack of clinical experience.

Although specific interaction studies were not performed, FOSAMAX® 10 mg/day was used concomitantly in postmenopausal osteoporosis studies with a wide range of commonly prescribed drugs without evidence of clinical adverse interactions.

The risk of upper gastrointestinal adverse events associated with NSAIDs does not appear to be greater with concomitant treatment with FOSAMAX® 10 mg/day. However, in patients receiving concomitant therapy with doses of FOSAMAX® greater than 10 mg/day and ASA-containing compounds, the incidence of upper gastrointestinal adverse events was increased.

Animal studies have demonstrated that FOSAMAX® is highly concentrated in bone and is retained only minimally in soft tissue. No metabolites have been detected. Although alendronate is bound approximately 78% to plasma protein in humans, its plasma concentration is so low after oral dosing that only a small fraction of plasma-binding sites is occupied, resulting in a minimal potential for interference with the binding of other drugs. Alendronate is not excreted through the acidic or basic transport systems of the kidney in rats, and thus it is not anticipated to interfere with the excretion of other drugs by those systems in humans. In summary, FOSAMAX® is not expected to interact with other drugs based on effects on protein binding, renal excretion, or metabolism of other drugs.

ADVERSE REACTIONS

FOSAMAX® (alendronate sodium) has been generally well tolerated. Side effects, which usually have been mild, generally have not required discontinuation of therapy.

Osteoporosis in postmenopausal women

FOSAMAX® has been evaluated for safety in clinical studies in more than 1800 postmenopausal patients. In two large, three-year, placebo-controlled, double-blind, multicenter studies (United States and Multinational) of virtually identical design, with a total of 994 post-menopausal women, the overall safety profiles of FOSAMAX® 10 mg/day and placebo were similar. Discontinuation of therapy due to any clinical adverse experience occurred in 4.1% of 196 patients treated with FOSAMAX® 10 mg/day and 6.0% of 397 patients treated with placebo.

Adverse experiences reported by the investigators as possibly, probably, or definitely drug-related in ≥ 1% of patients treated with either FOSAMAX® 10 mg/day or placebo are presented in the following table.

Drug-Related* Adverse Experiences Reported in ≥1% of Patients

	FOSAMAX® 10 mg/day % (n=196)	PLACEBO % (n=397)
Gastrointestinal		
abdominal pain	6.6	4.8
nausea	3.6	4.0
dyspepsia	3.6	3.5
constipation	3.1	1.8
diarrhea	3.1	1.8
flatulence	2.6	0.5
acid regurgitation	2.0	4.3
esophageal ulcer	1.5	0.0
vomiting	1.0	1.5
dysphagia	1.0	0.0
abdominal distention	1.0	0.8
gastritis	0.5	1.3
Musculoskeletal		
musculoskeletal pain	4.1	2.5
muscle cramp	0.0	1.0
Nervous System/Psychiatric		
headache	2.6	1.5
dizziness	0.0	1.0
Special Senses		
taste perversion	0.5	1.0

* Considered possibly, probably, or definitely drug-related as assessed by the investigators.

Rarely, rash and erythema have occurred.

One patient treated with FOSAMAX® (10 mg/day), who had a history of peptic ulcer disease and gastrectomy and who was taking concomitant ASA developed an anastomotic ulcer with mild hemorrhage, which was considered drug-related. ASA and FOSAMAX® were discontinued and the patient recovered.

Paget's disease

In clinical studies, adverse experiences reported in 175 patients taking FOSAMAX® 40 mg/day for 3 - 12 months were similar to those in post-menopausal women treated with FOSAMAX® 10 mg/day. However, there was an apparent increased incidence of upper gastrointestinal adverse experiences in patients taking FOSAMAX® 40 mg/day (17.7% FOSAMAX® vs 10.2% placebo). Isolated cases of esophagitis and gastritis resulted in discontinuation of treatment.

Additionally, musculoskeletal pain, which has been described in patients with Paget's disease treated with other bisphosphonates, was reported by the investigators as possibly, probably, or definitely drug-related in approximately 6% of patients treated with FOSAMAX® 40 mg/day versus approximately 1% of patients treated with placebo, but rarely resulted in discontinuation of therapy. Discontinuation of therapy due to any clinical adverse experience occurred in 6.4% of patients with Paget's disease treated with FOSAMAX® 40 mg/day and 2.4% of patients treated with placebo.

Laboratory Tests
In double-blind, multicenter, controlled studies, asymptomatic, mild, and transient decreases in serum calcium and phosphate were observed in approximately 18 and 10%, respectively, of patients taking FOSAMAX® versus approximately 12 and 3% of those taking placebo. However, the incidences of decreases in serum calcium to < 8.0 mg/dL (2.0 mM) and serum phosphate to ≤ 2.0 mg/dL (0.65 mM) were similar in both treatment groups.

In a small, open label study, at higher doses (80 mg/day) some patients had elevated transaminases. However, this was not observed at 40 mg/day. No clinically significant toxicity was associated with these laboratory abnormalities.

Rare cases of leukemia have been reported following therapy with other bisphosphonates. Any causal relationship to either the treatment or to the patients' underlying disease has not been established.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

No specific information is available on the treatment of overdosage with FOSAMAX® (alendronate sodium). Hypocalcemia, hypophosphatemia, and upper gastrointestinal adverse events, such as upset stomach, heartburn, esophagitis, gastritis, or ulcer, may result from oral overdosage. Administration of milk or antacids, to bind alendronate, should be considered.

Dialysis would not be beneficial.

DOSAGE AND ADMINISTRATION

FOSAMAX® (alendronate sodium) must be taken at least one-half hour before the first food, beverage, or medication of the day with a full glass of plain water only, since other beverages (including mineral water), food, and some medications are known to reduce the absorption of FOSAMAX® (see DRUG INTERACTIONS). Waiting longer than 30 minutes before eating will improve the absorption of FOSAMAX®. Waiting less than 30 minutes will lessen the effect of FOSAMAX® by decreasing its absorption into the body. To facilitate delivery to the stomach, FOSAMAX® should be taken with a full glass of water (6-8 oz) and patients should avoid lying down for at least 30 minutes thereafter.

Patients with osteoporosis or Paget's disease must receive supplemental calcium and vitamin D, if dietary intake is inadequate.

Although no specific studies have been conducted on the effects of switching patients on another therapy for osteoporosis or Paget's disease to FOSAMAX®, there are no known or theoretical safety concerns related to FOSAMAX® in patients who previously received any other anti-osteoporotic or antipagetic therapy.

Treatment with FOSAMAX® for longer than four years has not been studied; extension studies are ongoing.

No dosage adjustment is necessary for the elderly or for patients with mild-to-moderate renal insufficiency (creatinine clearance 35 to 60 mL/min). FOSAMAX® is not recommended for patients with more severe renal insufficiency (creatinine clearance < 35 mL/min).

Osteoporosis in Postmenopausal Women
The recommended dosage is 10 mg once a day.

Paget's Disease of Bone
The recommended treatment regimen is 40 mg once a day for six months.

Retreatment of Paget's Disease
In clinical studies in which patients were followed every six months, relapses during the 12 months following therapy occurred in 9% (3 out of 32) of patients who responded to treatment with FOSAMAX®. Specific retreatment data are not available, although responses to FOSAMAX® were similar in patients who had received prior bisphosphonate therapy and those who had not. Retreatment with FOSAMAX® may be considered, following a six month post-treatment evaluation period, both in patients who have relapsed (based on increases in serum alkaline phosphatase which should be measured periodically) and in those who failed to normalize their serum alkaline phosphatase.

Information to be Provided to the Patient
Patients must be instructed that the expected benefits of FOSAMAX® may only be obtained when each tablet is taken first thing in the morning at least 30 minutes before the first food, beverage or medication of the day with a full glass of plain water. Even dosing with orange juice or coffee has been shown to markedly reduce the absorption of FOSAMAX®.

AVAILABILITY OF DOSAGE FORMS

3600 Ca - FOSAMAX® 10 mg tablets, a white, round uncoated tablet with an embossed bone image on each side and FOSAMAX engraved on one side and MRK 936 on the other. Available in blister packages of 30 tablets.

3592 Ca - FOSAMAX® 40 mg tablets, a white, triangle-shaped uncoated tablet with FOSAMAX on one side and MRK 212 on the other. Available in blister packages of 30 tablets.

PRODUCT MONOGRAPH AVAILABLE ON REQUEST

(442-a,12,95)

9410, 9411, 9412, 9413

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℞ ZOCOR®

(simvastatin tablets)

Tablets 5, 10 and 20 mg

Cholesterol-lowering agent

INDICATIONS AND CLINICAL USE

As an adjunct to diet for the reduction of elevated total and LDL-C levels in patients with primary hypercholesterolemia; also in combined hypercholesterolemia and hypertriglyceridemia, when hypercholesterolemia is the abnormality of most concern.

To determine which patients to treat, initially establish that the elevation in plasma lipids is not due to underlying conditions such as poorly-controlled diabetes mellitus, hypothyroidism, the nephrotic syndrome, liver disease, or dysproteinemias. Then ascertain whether elevated LDL-C level is the cause for elevated total serum cholesterol, particularly in patients with total triglycerides over 4.52 mmol/L (400 mg/dL) or with markedly elevated HDL-C values, where non-LDL lipoprotein fractions may contribute significantly to total cholesterol levels, without apparent increase in cardiovascular risk.

CONTRAINDICATIONS

Hypersensitivity to any component. Active liver disease or unexplained persistent elevations of serum transaminases. Pregnancy and lactation (see PRECAUTIONS).

WARNINGS

The effects of simvastatin-induced changes in lipoprotein levels, including reduction of serum cholesterol, on cardiovascular morbidity or mortality have not been established.

1. Hepatic effects: In clinical trials, marked persistent increases in serum transaminases occurred in 1% of adult patients who received simvastatin (see ADVERSE REACTIONS). Increases were not associated with jaundice or other clinical signs or symptoms. There was no evidence of hypersensitivity. Serum transaminases fell slowly to pre-treatment levels when drug was interrupted or discontinued.

All patients should have liver function tests at baseline and periodically thereafter. Patients who develop elevated serum transaminase levels require special attention, prompt retesting and more frequent testing.

Discontinue drug if transaminase levels show evidence of progression, particularly a rise to 3 times the upper limit of normal that persists.

Use with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Discontinue drug if active liver disease or unexplained persistent transaminase elevations develop during therapy (see CONTRAINDICATIONS).

Moderate elevations of serum transaminases, reported with simvastatin, have also been observed with other, comparative lipid-lowering agents. These changes generally appeared within the first 3 months after initiation of therapy, were often transient, not accompanied by any symptom, and did not need interruption of treatment.

2. Muscle Effects - CPK: Transient elevation of creatine phosphokinase (CPK) levels commonly seen, usually have no clinical significance. **- Myalgia** and muscle cramps have also been observed. **- Myopathy** reported rarely (0.05%); consider possibility in any patient with diffuse myalgias, muscle tenderness and/or marked elevation of creatine phosphokinase (≥ 10 times the upper limit of normal). Ask patients to promptly report unexplained muscle pain, tenderness and weakness. With *lovastatin*, a closely related HMG-CoA reductase inhibitor, the risk of myopathy is known to be substantially increased by concomitant immunosuppressive drugs including cyclosporins, or gemfibrozil or lipid-lowering doses of niacin. Severe rhabdomyolysis that precipitated acute renal failure was reported. Also, rhabdomyolysis with or without renal impairment was reported in seriously ill patients receiving concomitant erythromycin and lovastatin.

Therefore, carefully consider benefits and risks of concomitant use of simvastatin with immunosuppressive drugs, fibrates, erythromycin or lipid-lowering doses of niacin. Consider interrupting simvastatin in any patient with an acute, serious condition, suggestive of a myopathy or a risk factor predisposing to development of renal failure or rhabdomyolysis, such as: severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine or electrolyte disorders and uncontrolled seizures.

PRECAUTIONS

General: Before starting therapy, attempt to control hypercholesterolemia with appropriate diet, exercise, weight reduction in overweight and obese patients, and to treat underlying medical problems (see INDICATIONS). The patient should inform subsequent physicians of prior use of simvastatin. **Ophthalmic evaluations:** Current data do not indicate adverse effects on the human lens, but long-term effects have not been established. Periodic ophthalmological exams are recommended, keeping in mind that even without drugs, an increased prevalence in lens opacities could be expected with aging. **Use in homozygous familial hypercholesterolemia:** simvastatin is unlikely to be of clinical benefit. **Effect on Lipoprotein(a) [Lp(a)]:** In some patients, the beneficial lowering of total and LDL cholesterol may be partly blunted by increased Lp(a) levels. Pending further experience, Lp(a) plasma levels should be measured when feasible in patients given simvastatin. **Hypersensitivity:** A few instances of eosinophilia and skin eruptions appear to be associated with simvastatin. If hypersensitivity suspected, discontinue drug. **Carcinogenesis:** In animal studies, increased incidences of hepatocellular adenomas and carcinomas, pulmonary adenomas and harderian gland adenomas were noticed in mice receiving 500 times the maximum recommended human dose. Female rats receiving 31 times the maximum recommended human dose exhibited an increased incidence of thyroid follicular adenomas. (See TOXICOLOGY Section of Product Monograph.)

Use in obstetrics: Simvastatin is contraindicated during pregnancy and there are no data on such use. Because the HMG-CoA reductase inhibitors are able to decrease the synthesis of cholesterol and possibly other products of the cholesterol biosynthesis pathway that are essential components for fetal development, simvastatin may cause fetal harm. Administer to women of childbearing age only when they are highly unlikely to conceive. If a patient becomes pregnant, apprise her of potential hazard to the fetus, and discontinue drug. **Nursing mothers:** Whether simvastatin is excreted in human milk is unknown. However, because of the potential for serious adverse reactions, women taking simvastatin should not nurse (see CONTRAINDICATIONS). **Pediatric use:** Safety and effectiveness have not been established; therefore simvastatin therapy in children is not yet recommended. **Use in patients with impaired renal function:** Exercise caution if renal function impairment is significant.

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Drug Interactions
Concomitant therapy with other lipid-lowering agents: Cholesterol-lowering effects of simvastatin and cholestyramine appear additive. Exercise caution when coadministering with other lipid-lowering agents, particularly gemfibrozil and niacin (see WARNINGS). **Erythromycin:** See WARNINGS: Muscle effects. **ACE Inhibitors:** Hyperkalemia associated with myositis was reported in a single patient with insulin-dependent diabetes mellitus and mild renal insufficiency who received another HMG-CoA reductase inhibitor: lovastatin with an ACE inhibitor, lisinopril. **Coumarin anticoagulants:** Determine prothrombin time in patients on concomitant coumarin anticoagulants before starting simvastatin therapy and monitor periodically, because anticoagulant effect of warfarin appeared to be slightly enhanced by simvastatin use. **Digoxin:** Digoxin plasma concentrations were slightly elevated by coadministration of simvastatin. **Propranolol:** No clinically significant pharmacokinetic or pharmacodynamic interaction noted with concomitant simvastatin. **Antipyrine:** Simvastatin had little or no effect on the pharmacokinetics of antipyrine. **Other concomitant therapy:** Exercise caution with coadministration of immunosuppressants (see WARNINGS). In clinical studies, simvastatin was used with beta-blockers, calcium-channel blockers, diuretics and NSAIDs, without evidence of clinically significant adverse interactions.

Drug/laboratory test interactions: Simvastatin may elevate serum transaminase and creatine phosphokinase levels (see ADVERSE REACTIONS). In differential diagnosis of chest pain in patients on simvastatin, determine cardiac and non-cardiac fractions of these enzymes.

ADVERSE REACTIONS

Simvastatin was found generally well tolerated, and adverse reactions usually mild and transient, based on experience in over 2300 patients, of whom over 1200 were treated for 1 year and over 230 for 2 years or more. In controlled clinical trials, 1% were withdrawn due to adverse experiences attributable to simvastatin. Adverse experiences occurring at an incidence of ≥0.5% of 2361 patients treated with simvastatin in controlled clinical studies and reported to be possibly, probably or definitely drug related are shown in the table below:

	ZOCOR® (n = 2361) %
Gastrointestinal	
Acid Regurgitation	0.5
Constipation	2.5
Dyspepsia	0.6
Diarrhea	0.8
Flatulence	2.0
Nausea	1.1
Nervous System	
Headache	1.0
Skin	
Rash	0.7
Miscellaneous	
Abdominal Pain	2.2
Asthenia	0.8

Ophthalmological Observations: see PRECAUTIONS.

Laboratory tests: Marked persistent increases of serum transaminases noted (see WARNINGS). About 5% of patients had elevations of CPK levels of at least three times normal value, attributable to the non-cardiac fraction of CPK, on one or more occasions. Myopathy reported rarely (see WARNINGS and PRECAUTIONS).

Others: Though not observed in clinical trials with simvastatin, the following have been reported with other HMG-CoA reductase inhibitors: hepatitis, cholestatic jaundice, vomiting, anorexia, paresthesia, psychic disturbances including anxiety, and hypospermia. Also reported rarely with lovastatin was a hypersensitivity syndrome which included one or more of the following: anaphylaxis, angioedema, lupus-like syndrome, polymyalgia rheumatica, thrombocytopenia, leukopenia, hemolytic anemia, positive ANA, ESR increase, arthritis, arthralgia, urticaria, asthenia, photosensitivity, fever and malaise.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

No experience of deliberate or accidental overdosage. **Treatment** should be symptomatic and supportive, liver function should be monitored, and appropriate therapy instituted. Dialyzability of simvastatin not known.

DOSAGE AND ADMINISTRATION

Before initiating simvastatin, place patient on standard cholesterol-lowering diet, and continue on this diet during treatment. If appropriate, implement a program of weight control and exercise. **Usual starting dose**: 10 mg/day, as a single dose in the **evening.** Make dosage adjustments, if necessary, at intervals of not less than 4 weeks, to **maximum** of 40 mg daily, given as a single evening dose. **Monitor cholesterol levels periodically and consider reducing dosage if cholesterol levels fall below targeted range, as recommended by the Canadian Consensus Conference on Cholesterol.**

Concomitant therapy: Cholesterol-lowering effects of simvastatin and cholestyramine appear additive. For use with other lipid-lowering agents, see WARNINGS and PRECAUTIONS.

AVAILABILITY AND DOSAGE FORMS

ZOCOR® Tablets are shield-shaped, film-coated, engraved with a code on one side and Z on the other. ZOCOR® 5 mg and 10 mg tablets are available in blister packs of 30 tablets. 10 mg tablets available in bottles of 500s. 20 mg tablets available in bottles of 100s.

- ZOCOR® 5 mg, buff tablet, engraved 726.
- ZOCOR® 10 mg, peach tablet, engraved 735.
- ZOCOR® 20 mg, tan tablet, engraved 740.

PRODUCT MONOGRAPH AVAILABLE ON REQUEST

(508x-a,7,94)

References:

1. The Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383-89.

8526, 8582, 8592

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Pr BIAXIN®
CLARITHROMYCIN

PRESCRIBING INFORMATION

NAME OF DRUG: BIAXIN® (clarithromycin film-coated tablets)
(clarithromycin pediatric granules for suspension)

THERAPEUTIC CLASSIFICATION: Antibiotic

ACTIONS AND CLINICAL PHARMACOLOGY

BIAXIN® (clarithromycin film-coated tablets and clarithromycin pediatric granules for suspension) exerts its antibacterial action by binding to the 50S ribosomal subunit of susceptible bacteria and suppressing protein synthesis.

BIAXIN® (clarithromycin film-coated tablets)

The absolute bioavailability of 250 mg and 500 mg clarithromycin tablets is approximately 50%. Food slightly delays the onset of clarithromycin absorption but does not affect the extent of bioavailability. Therefore, BIAXIN® tablets may be given without regard to meals.

In fasting healthy human subjects, peak serum concentrations are attained within 2 hours after oral dosing. Steady-state peak serum clarithromycin concentrations, which are attained within 2 to 3 days, are approximately 1 mg/L with a 250 mg dose twice daily and 2 to 3 mg/L with a 500 mg dose twice daily. The elimination half-life of clarithromycin is about 3 to 4 hours with 250 mg twice daily dosing but increases to about 5 to 7 hours with 500 mg administered twice daily.

The non-linearity of clarithromycin pharmacokinetics is slight at the recommended doses of 250 mg and 500 mg administered twice daily. With 250 mg twice daily, the principal metabolite, 14-OH-clarithromycin attains a peak steady state concentration of about 0.6 mg/L and has an elimination half-life of 5 to 6 hours. With a 500 mg twice daily dose, the peak steady-state of 14-OH concentrations of clarithromycin are slightly higher (up to 1 mg/L) and its elimination half-life is about 7 hours. With either dose, the steady-state concentration of this metabolite is generally attained within 2 to 3 days.

Steady-state concentrations of clarithromycin and 14-OH-clarithromycin observed following administration of 500 mg doses of clarithromycin twice a day to adult patients with HIV infection were similar to those observed in healthy volunteers. However, at the higher clarithromycin doses which may be required to treat mycobacterial infections, clarithromycin concentrations can be much higher than those observed at 500 mg clarithromycin doses. In adult HIV-infected patients taking 2000 mg/day in two divided doses, steady-state clarithromycin C_{max} values ranged from 5-10 mg/L. C_{max} values as high as 27 mg/L have been observed in HIV-infected adult patients taking 4000 mg/day in two divided doses of BIAXIN® tablets.

Elimination half-lives appeared to be lengthened at these higher doses as well. The higher clarithromycin concentrations and longer elimination half-lives observed at these doses are consistent with the known non linearity in clarithromycin pharmacokinetics.

BIAXIN® (clarithromycin pediatric granules for suspension)

Single and multiple dose adult volunteer studies showed that the suspension formulation was not significantly different from the tablet formulation in terms of C_{max} of clarithromycin and AUC, although the onset and/or rate of absorption of the suspension formulation was slower than that of the tablet. As with the tablet formulation, steady state is achieved by the fifth dose of a 12-hour multiple dose suspension regimen.

A single and multiple dose study conducted in pediatric patients showed that food leads to a slight delay in the onset of absorption, but does not affect the overall bioavailability of clarithromycin.

Clarithromycin and its 14-OH metabolite penetrate into middle ear effusion (MEE) of patients with secretory otitis media.

INDICATIONS AND CLINICAL USES

BIAXIN® (clarithromycin film-coated tablets)

BIAXIN® (clarithromycin film-coated tablets) may be indicated in the treatment of mild to moderate infections caused by susceptible strains of the designated microorganisms in the diseases listed below:

Upper respiratory tract: Pharyngitis/tonsillitis, caused by *Streptococcus pyogenes* (Group A beta-hemolytic streptococci).

Acute maxillary sinusitis caused by *Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella (Branhamella) catarrhalis.*

Lower respiratory tract: Acute bacterial exacerbation of chronic bronchitis caused by *Streptococcus pneumoniae, Haemophilus influenzae* (including beta-lactamase-producing strains), *Moraxella (Branhamella) catarrhalis* (including beta-lactamase-producing strains).

Pneumonia caused by *Streptococcus pneumoniae* and *Mycoplasma pneumoniae.*

Uncomplicated Skin and Skin Structure Infections caused by *Streptococcus pyogenes, Staphylococcus aureus.*

Mycobacterial Infections: BIAXIN (clarithromycin film-coated tablets) is indicated for the treatment of disseminated mycobacterial infections due to *Mycobacterium avium* and *Mycobacterium intracellulare.*

BIAXIN® (clarithromycin pediatric granules for suspension)

BIAXIN® (clarithromycin pediatric granules for suspension) is indicated for the treatment of infections due to susceptible organisms, in the following conditions:

- Upper Respiratory Tract:
  (1) Pharyngitis caused by *S. pyogenes* (Group A β-hemolytic streptococci).
  (2) Acute otitis media caused by *H. influenzae, M. catarrhalis,* or *S. pneumoniae.* (See CLINICAL STUDIES: Otitis media).
- Lower respiratory tract:
  Mild to moderate community-acquired pneumonia caused by *S. pneumoniae, C. pneumoniae,* or *M. pneumoniae.*
- Uncomplicated skin and skin structure infections (i.e., impetigo and cellulitis) caused by *S. aureus* or *S. pyogenes.*

CLINICAL STUDIES

Otitis Media: In a controlled clinical study of acute otitis media performed in the United States, where significant rates of beta-lactamase-producing organisms were found, clarithromycin was compared to an oral cephalosporin.

In a small number of patients, microbiologic determinations were made at the pre-treatment visit. The following presumptive bacterial eradications/clinical cure outcomes (i.e., clinical success) were obtained:

U.S. Acute Otitis Media Study
Clarithromycin vs. Oral Cephalosporin
EFFICACY RESULTS

PATHOGEN	OUTCOME
S. pneumoniae	clarithromycin success rate, 13/15 (87%), control 4/5
*H. influenzae**	clarithromycin success rate, 10/14 (71%), control 3/4
M. catarrhalis	clarithromycin success rate, 4/5, control 1/1
S. pyogenes	clarithromycin success rate, 3/3, control 0/1
Overall	clarithromycin success rate, 30/37 (81%), control 8/11 (73%)

*None of the *H. influenzae* isolated pre-treatment was resistant to clarithromycin; 6% were resistant to the control agent.

In two other controlled clinical trials of acute otitis media performed in the United States, where significant rates of beta-lactamase-producing organisms were found, clarithromycin was compared to an oral antimicrobial agent that contained a specific beta-lactamase inhibitor.

For the patients who had microbiologic determinations at the pre-treatment visit, the following presumptive bacterial eradication/clinical cure outcomes (i.e., clinical success) were obtained:

Two U.S. Acute Otitis Media Studies
Clarithromycin vs. Antimicrobial/Beta-Lactamase Inhibitor
EFFICACY RESULTS

PATHOGEN	OUTCOME
S. pneumoniae	clarithromycin success rate, 43/51 (84%), control 55/56 (98%)
*H. influenzae**	clarithromycin success rate, 36/45 (80%), control 31/33 (94%)
M. catarrhalis	clarithromycin success rate, 9/10 (90%), control 6/6
S. pyogenes	clarithromycin success rate, 3/3, control 5/5
Overall	clarithromycin success rate, 91/109 (83%), control 97/100 (97%)

*Of the *H. influenzae* isolated pre-treatment, 3% were resistant to clarithromycin and 10% were resistant to the control agent.

In the two U.S. acute otitis media studies of clarithromycin vs. antimicrobial/beta-lactamase inhibitor, the incidence of adverse events in all patients treated, primarily diarrhea (15% vs. 38%) and diaper rash (3% vs. 11%) in young children, was clinically or statistically lower in the clarithromycin arm vs. the control arm.

Appropriate culture and susceptibility tests should be performed prior to initiating treatment in order to isolate and identify organisms causing the infection and to determine their susceptibilities to BIAXIN®. Therapy with BIAXIN® may be initiated before results of these tests are known. However, modification of this treatment may be required once results become available or if there is no clinical improvement.

CONTRAINDICATIONS: BIAXIN® (clarithromycin film-coated tablets and clarithromycin pediatric granules for suspension) is contraindicated in patients with a known hypersensitivity to clarithromycin, erythromycin or other macrolide antibacterial agents.

BIAXIN® is contraindicated as concurrent therapy with astemizole or terfenadine. (See PRECAUTIONS: Drug Interactions).

WARNINGS: BIAXIN® (clarithromycin film-coated tablets and clarithromycin pediatric granules for suspension) should be administered with caution to any patient who has demonstrated some form of drug allergy, particularly to structurally related drugs. If an allergic reaction to clarithromycin occurs, administration of the drug should be discontinued. Serious hypersensitivity reactions may require epinephrine, antihistamines, or corticosteroids.

Pregnancy: BIAXIN® should not be used in pregnancy except where no alternative therapy is appropriate, particularly during the first 3 months of pregnancy. If pregnancy occurs while taking the drug, the patient should be apprised of the potential hazard to the fetus. Clarithromycin has demonstrated adverse effects on pregnancy outcome and/or embryo-fetal development in monkeys, mice, rats and rabbits at doses that produced plasma levels 2 to 17 times the serum levels obtained in humans treated at the maximum recommended doses.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including macrolides, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents, including BIAXIN®. Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is a primary cause of "antibiotic-associated colitis".

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to discontinuation of the drug alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug effective against *Clostridium difficile.*

PRECAUTIONS: Clarithromycin is principally excreted by the liver and kidney. (See DOSAGE AND ADMINISTRATION). In patients with both hepatic and renal impairments or in the presence of severe renal impairment, decreased dosage of BIAXIN® (clarithromycin film-coated tablets and clarithromycin pediatric granules for suspension) or prolonged dosing intervals might be appropriate.

Drug Interactions:

Theophylline: BIAXIN® use in patients who are receiving theophylline may be associated with an increase of serum theophylline concentrations. Monitoring of serum theophylline concentrations should be considered for patients receiving high doses of theophylline or with baseline concentrations in the upper therapeutic range.

Carbamazepine: Clarithromycin administration in patients receiving carbamazepine has been reported to cause increased levels of carbamazepine. Blood level monitoring of carbamazepine may be considered.

Terfenadine: Macrolides have been reported to alter the metabolism of terfenadine resulting in increased serum levels of terfenadine which have occasionally been associated with cardiac arrhythmias.

In a study involving 14 healthy volunteers, the concomitant administration of BIAXIN® tablets and terfenadine resulted in a two to three-fold increase in the serum level of the acid metabolite of terfenadine, MDL 16, 455, and in prolongation of the QT interval which did not lead to any clinically detectable effect. (See CONTRAINDICATIONS).

Zidovudine: Simultaneous oral administration of BIAXIN® tablets and zidovudine to HIV-infected adult patients may result in decreased steady-state zidovudine concentrations. Clarithromycin appears to interfere with the absorption of simultaneously administered oral zidovudine, therefore this interaction can be largely avoided by staggering the doses of clarithromycin and zidovudine.

Digoxin: Elevated digoxin serum concentrations have been reported in patients receiving BIAXIN® tablets and digoxin concomitantly. Monitoring of serum digoxin levels should be considered.

Attention should be paid to the possibility of cross resistance between BIAXIN® and other macrolide drugs, as well as lincomycin and clindamycin.

As with other macrolide antibiotics, the use of BIAXIN® in patients concurrently taking drugs metabolized by the cytochrome P_{450} system (e.g., warfarin, ergot alkaloids, triazolam, midazolam, and cyclosporine) may be associated with elevations in serum levels of these other drugs.

The following drug interactions have not been reported in clinical trials with clarithromycin; however, they have been observed with another macrolide, erythromycin:

Concomitant administration of erythromycin and digoxin has been reported to result in elevated digoxin levels.

There have been reports of increased anticoagulant effects when erythromycin and oral anticoagulants were used concomitantly.

Concurrent use of erythromycin and ergotamine or dihydroergotamine has been associated in some patients with acute ergot toxicity characterized by ischemic reactions.

Erythromycin has been reported to decrease the clearance of triazolam and midazolam and thus may increase the pharmacologic effect of triazolam and midazolam.

The use of erythromycin in patients concurrently taking drugs metabolized by the cytochrome P_{450} system may be associated with elevations in serum levels of these other drugs. There have been reports of interactions of erythromycin with cyclosporine, hexobarbital, valproate, phenytoin, alfentanil, disopyramide, bromocriptine, terfenadine or astemizole. Serum concentrations of drugs metabolized by the cytochrome P_{450} system should be monitored closely in patients concurrently receiving erythromycin.

Pregnancy: There are no adequate and well-controlled studies in pregnant women. The benefits against risk, particularly during the first 3 months of pregnancy should be carefully weighed by a physician. (See WARNINGS). Four teratogenicity studies in rats (three with oral doses and one with intravenous doses up to 160 mg/kg/day administered during the period of major organogenesis) and two in rabbits (at oral doses up to 125 mg/ kg/day or intravenous doses of 30 mg/kg/day administered during gestation days 6 to 18) failed to demonstrate any teratogenicity from clarithromycin. Two additional oral studies in a different rat strain at similar doses and similar conditions demonstrated a low incidence of cardiovascular anomalies at doses of 150 mg/kg/day administered during gestation days 6 to 15. Plasma levels after 150 mg/kg/day were 2 times the human serum levels. Four studies in mice revealed a variable incidence of cleft palate following oral doses of 1000 mg/kg/day during gestation days 6 to 15. Cleft palate was also seen at 500 mg/kg/day. The 1000 mg/kg/day exposure resulted in plasma levels 17 times the human serum levels. In monkeys, an oral dose of 70 mg/kg/day produced fetal growth retardation at plasma levels that were 2 times the human serum levels. Embryonic loss have been seen in monkeys and rabbits.

Nursing Mothers: The safety of BIAXIN® for use during breastfeeding of infants has not been established. Clarithromycin is excreted in human milk.

Pediatric Use: Use of clarithromycin tablets in children under 12 years of age has not been studied.

Use of clarithromycin granules for suspension in children under 6 months has not been studied. In pneumonia, clarithromycin granules were not studied in children younger than 3 years.

Increased valproate and phenobarbital concentrations and extreme sedation were noted in a 3-year-old patient coincident with clarithromycin therapy. Cause and effect relationship cannot be established. However, monitoring of valproate and phenobarbital concentrations may be considered.

Geriatric Use: Dosage adjustment should be considered in elderly patients with severe renal impairment. In a steady-state study in which healthy elderly subjects (age 65 to 81 years old) were given 500 mg every 12 hours, the maximum concentrations of clarithromycin and 14-OH-clarithromycin were increased. The AUC was also increased. These changes in pharmacokinetics parallel known age-related decreases in renal function. In clinical trials, elderly patients did not have an increased incidence of adverse events when compared to younger patients.

ADVERSE REACTIONS

BIAXIN® (clarithromycin film-coated tablets)

Patients with Respiratory Tract or Skin Infections: The majority of side effects observed in clinical trials involving 3563 patients treated with BIAXIN® were of a mild and transient nature. Fewer than 3% of adult patients without mycobacterial infections discontinued therapy because of drug-related side effects. During these clinical studies the following adverse reactions were reported:

BODY AS A WHOLE – headache (2%), asthenia, infection, back pain, pain and chest pain.

DIGESTIVE SYSTEM – nausea (4%), diarrhea (3%), abdominal pain (2%), dyspepsia (2%), vomiting (1%), constipation, flatulence, dry mouth, stomatitis, gastrointestinal disorder, anorexia, oral moniliasis and hepatomegaly.

NERVOUS SYSTEM – dizziness, vertigo, nervousness, anxiety, insomnia, nightmares, somnolence, depression, confusion and hallucinations.

RESPIRATORY SYSTEM – rhinitis, cough increased, dyspnea, pharyngitis and asthma.

SKIN AND APPENDAGES – pruritus, rash, sweating; allergic reactions including urticaria ranging from mild skin eruptions to anaphylaxis and Stevens-Johnson Syndrome have occurred with orally administered clarithromycin.

SPECIAL SENSES – taste perversion (2%) , ear disorder, abnormal vision and conjunctivitis.

UROGENITAL SYSTEM – hematuria, vaginal moniliasis, vaginitis and dysmenorrhea.

HEMIC AND LYMPHATIC SYSTEM – eosinophilia, anemia, leukopenia and thrombocythemia.

CHANGES IN LABORATORY VALUES: Changes in laboratory values with possible clinical significance were as follows:

Hepatic – elevated SGPT < 1%, SGOT < 1%, GGT < 1%, alkaline phosphatase < 1%, LDH < 1% and total bilirubin < 1%.

Hematologic – decreased WBC < 1% and elevated prothrombin time (1%).

Renal – elevated BUN (4%) and elevated serum creatinine < 1%.

OTHERS: The following adverse reactions have not been observed in clinical trials with BIAXIN® but they have been occasionally reported with erythromycin, another macrolide: Pseudomembranous colitis, cardiac arrhythmias such as ventricular tachycardia and torsades de pointes in individuals with prolonged QT intervals, central nervous system side effects (including seizures, hallucinations, confusion and vertigo), anaphylaxis, and reversible hearing loss occurring chiefly in patients with renal insufficiency and in patients receiving high doses of erythromycin.

As with other macrolides, hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been infrequently reported with BIAXIN®. This hepatic dysfunction may be severe and is usually reversible. In very rare instances, hepatic failure with fatal outcome has been reported and generally has been associated with serious underlying diseases and/or concomitant medications.

In studies of adults with pneumonia comparing clarithromycin to erythromycin base or erythromycin stearate, there were significantly fewer adverse events involving the digestive system in patients treated with clarithromycin.

Rarely, erythromycin has been associated with ventricular arrhythmias, including ventricular tachycardia, and torsade de pointes, in individuals with prolonged QT intervals.

Glossitis, stomatitis and oral monilia have been reported with BIAXIN® therapy.

Patients with Mycobacterial Infections: In AIDS and other immunocompromised patients treated with the higher doses of clarithromycin over long periods of time for mycobacterial infections, it was often difficult to distinguish adverse events possibly associated with clarithromycin administration from underlying signs of HIV disease or intercurrent illness. Excluding those patients who discontinued therapy due to complications of their underlying non-mycobacterial diseases (including death), approximately 14% of the patients discontinued therapy due to drug-related adverse events.

In adult patients, the most frequently reported adverse events with an incidence of 3% or greater, excluding those due to the patient's concurrent condition, are listed in Table 1 by the total daily dose the patient was receiving at the time of the event. A total of 867 patients were treated with clarithromycin for mycobacterial infections. Of these, 43% reported one or more adverse events. Most of these events were described as mild to moderate in severity, although 14% were described as severe. Incidence of adverse events was higher in patients taking 4000 mg doses compared to lower doses.

Table 1
Percentage of Adverse Events* in Immunocompromised Adult Patients Treated with Clarithromycin for Mycobacterial Infections

	Presented by Total Daily Dose at Time of the Event		
	1000 mg	2000 mg	4000 mg
Adverse Event	(n = 463)	(n = 516)	(n = 87)
Nausea	11%	16%	40%
Vomiting	7%	9%	24%
Taste Perversion	6%	7%	29%
Abdominal Pain	5%	7%	20%
Diarrhea	4%	6%	17%
Rash	4%	3%	2%
SGOT Increased	2%	2%	11%
Flatulence	1%	2%	7%
Headache	2%	2%	7%
Constipation	1%	< 1%	5%
SGPT Increased	1%	1%	9%
Dyspnea	< 1%	< 1%	7%
Insomnia	< 1%	< 1%	6%
Hearing Disturbance**	3%	2%	5%
Dry Mouth	< 1%	0%	5%

*Related adverse events considered to be definitely, probably, possibly or remotely related to study events.

**Sum of patients with deafness, ear disorder, partial transitory deafness, and/or tinnitus.

n = Number of adverse events.

Changes in Laboratory Values: In immunocompromised patients treated with clarithromycin for mycobacterial infections, evaluations of laboratory values were made by analysing those values outside the seriously abnormal level (i.e., the extreme high or low limit) for the specified test. (See Table 2)

Table 2
Percentage of Immunocompromised Adult Patients Treated with Clarithromycin for Mycobacterial Infections who had On-treatment Laboratory Values that were Outside the Seriously Abnormal Level

		Presented by Total Daily Dose		
	Seriously Abnormal			
Parameter	Level	1000 mg	2000 mg	4000 mg
SGOT	> 5 x ULN*	3%	2%	4%
SGPT	> 5 x ULN*	2%	2%	7%
Platelets	< 50 x 10^9/L	2%	2%	4%
WBC	< 1 x 10^9/L	0%	2%	0%
BUN	> 50 mg/dL	< 1%	< 1%	4%

* ULN = Upper Limit of Normal.

BIAXIN® (clarithromycin pediatric granules for suspension)

The safety profile of BIAXIN® (clarithromycin pediatric granules for suspension) is similar to that of the 250 mg tablet in adult patients.

As with other macrolides, hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been infrequently reported with BIAXIN®. This hepatic dysfunction may be severe and is usually reversible. In very rare instances, hepatic failure with fatal outcome has been reported and generally has been associated with serious underlying diseases and/or concomitant medications.

Glossitis, stomatitis and oral monilia have been reported with BIAXIN® therapy.

571/1829 (31%) of the patients who received clarithromycin pediatric granules reported at least one adverse event. The adverse events reported are summarized in Table 3:

Table 3: Adverse Events Reported in Pediatric Clinical Trials

Body System	Number (%) of Patients (n = 1829)
Body as a Whole	168 (9%)
Cardiovascular	2 (< 1%)
Digestive	302 (17%)
– gastrointestinal	285
– other digestive	29
Haemic/Lymphatic	15 (1%)
Metabolic/Nutritional	21 (1%)
Musculoskeletal	2 (< 1%)
Nervous	21 (1%)
Respiratory	120 (7%)
Skin and Appendages	69 (4%)
Special Senses	52 (3%)
Urogenital	6 (< 1%)
TOTAL*	**571 (31%)**

* Patients with more than one event within a body system are only counted once in the total for that body system. Patients with events in more than one body system are counted only once in the overall total.

The majority of the patients with adverse events reported events in the digestive (302; 17%) and body as a whole (168; 9%) body systems.

The events occurring most frequently in the digestive system were gastrointestinal events of which diarrhea (7%), vomiting (7%), abdominal pain (3%), dyspepsia (3%) and nausea (1%) were the most common. Other adverse events included infection (3%), rhinitis (2.2%), rash (2.2%), increased cough (2.1%), fever (2.2%), headache (1.6%), conjunctivitis (1.1%), taste perversion (3%) and transient elevation of SGOT (0.9%). The majority of adverse events were considered by the investigators to have either mild or moderate severity. 375/1829 patients (21%) had mild adverse events, 175/1829 patients (10%) had moderate adverse events and 20/1829 patients (1%) had severe adverse events. In the two U.S. acute otitis media studies of clarithromycin vs. antimicrobial/beta-lactamase inhibitor, the incidence of adverse events in all patients treated, primarily diarrhea (15% vs. 38%) and diaper rash (3% vs.11%) in young children, was clinically or statistically lower in the clarithromycin arm vs. the control arm.

In another U.S. otitis media study of clarithromycin vs. cephalosporin, the incidence of adverse events in all patients treated, primarily diarrhea and vomiting, did not differ clinically or statistically for the two agents.

SYMPTOMS AND TREATMENT OF OVERDOSAGE: Reports indicate that the ingestion of large amounts of clarithromycin can be expected to produce gastrointestinal symptoms. Adverse reactions accompanying overdosage should be treated by the prompt elimination of unabsorbed drug and supportive measures.

Clarithromycin is protein bound (70%). No data are available on the elimination of clarithromycin by hemodialysis or peritoneal dialysis.

DOSAGE AND ADMINISTRATION: BIAXIN® (clarithromycin film-coated tablets and pediatric granules for suspension) may be given with or without meals.

BIAXIN® (clarithromycin film-coated tablets)

Adults with Respiratory Tract or Skin Infections: The usual adult dosage is 250 mg to 500 mg every 12 hours (See Table 4) for 7 to 14 days.

Table 4: Dosage Guidelines

Infection	Dosage (b.i.d.)
Upper Respiratory Tract	**250-500 mg**
Pharyngitis/tonsilitis	250 mg
Acute maxillary sinusitis	500 mg
Lower Respiratory Tract	**250-500 mg**
Acute exacerbation of chronic bronchitis and pneumonia	
Uncomplicated Skin and Skin Structure Infections	**250 mg**

For more severe infections or those caused by less susceptible organisms, the upper dosage should be used. In the treatment of Group A streptococcus infections, therapy should be continued for 10 days. The usual drug of choice in the treatment of streptococcal infections and the prophylaxis of rheumatic fever is penicillin administered by either the I.M. or the oral route. Clarithromycin is generally effective in the eradication of *S. pyogenes* from the nasopharynx; however, data establishing the efficacy of clarithromycin in the subsequent prevention of rheumatic fever are not presently available.

In patients with renal impairment and a creatinine clearance less than 30 mL/min., the dosage of BIAXIN® should be reduced by one-half, i.e., 250 mg once daily, or 250 mg twice daily in more severe infections. Dosage should not be continued beyond 14 days in these patients. In patients with both hepatic and renal impairments or in the presence of severe renal impairment, decreased dosage of BIAXIN® or prolonged dosing intervals may be appropriate. Clarithromycin may be administered without dosage adjustment in the presence of hepatic impairment if there is normal renal function.

Adults with Mycobacterial Infections: Clarithromycin is recommended as the primary agent for the treatment of disseminated infection due to *Mycobacterium avium* complex. Clarithromycin should be used in combination with other antimycobacterial drugs which have shown *in vitro* activity against MAC, including ethambutol, clofazimine, and rifampin. Although no controlled clinical trial information is available for combination therapy with clarithromycin, the U.S. Public Health Service Task Force has provided recommendations for the treatment of MAC.

The recommended dose for mycobacterial infections in adults is 500 mg b.i.d.

Treatment of disseminated MAC infections in AIDS patients should continue for life if clinical and mycobacterial improvement are observed.

BIAXIN® (clarithromycin pediatric granules for suspension)

The recommended daily dosage of BIAXIN® (clarithromycin pediatric granules for suspension) is 15 mg/kg/day, in divided doses every 12 hours, not to exceed 1000 mg/day. The usual duration of treatment is for 5 to 10 days depending on the pathogen involved and the severity of the condition. Treatment for pharyngitis caused by *Streptococcus* spp. should be 10 days.

In children with renal impairment and a creatinine clearance less than 30 mL/min., the dosage of BIAXIN® should be reduced by one-half, i.e., 250 mg once daily, or 250 mg twice daily in more severe infections. Dosage should not be continued beyond 14 days in these patients.

Table 5 is a suggested guide for determining dosage:

Table 5: Based on Body Weight in kg

Weight*	Dosage in standard 5 mL teaspoonfuls given twice daily
8-11 kg (1-2 years)**	0.5
12-19 kg (2-4 years)	1.0
20-29 kg (4-8 years)	1.5
30-40 kg (8-12 years)	2.0

*Children < 8 kg should be dosed on a per kg basis (approximately 7.5 mg/kg b.i.d.).

** Approximate ages.

The reconstituted suspension must not be refrigerated.

PHARMACEUTICAL INFORMATION

Drug Substance

Proper Names: Clarithromycin

USAN Names: Clarithromycin, 6-0-methyl-erythromycin

Chemical Name: (3R*, 4S*, 5S*, 6R*, 7R*, 9R*, 11R*, 12R*, 13S*, 14R*)-4-[(2,6-dideoxy-3-C-methyl-3-0-methyl-alpha-L-ribo-hexopyranosyl)oxy]-14-ethyl-12,13-dihydroxy-7-methoxy-3,5,7,9,11,13-hexamethyl-6-[[3,4,6-trideoxy-3-(dimethylamino)-beta-D-xylo-hexopyranosyl]oxy]oxacyclotetradecane-2-10-dione.

Molecular Weight: 747.96 *Molecular Formula:* $C_{38}H_{69}NO_{13}$

Description: Clarithromycin is a white to off-white crystalline powder. It is slightly soluble in methanol, ethanol and acetonitrile, and practically insoluble in water. The pKa of clarithromycin is 8.48; the pH of a 0.2% (Methanol:Water, 5:95) slurry is 8.8. The partition coefficient of clarithromycin is influenced by the pH of the water phase and polarity of the organic phase. For octanol (dipole moment = 0.25): water, the partition coefficient varies from 5.63 to 46.0 for pH water increases from 2 to 8. The melting point of clarithromycin is approximately 225°C.

Composition: BIAXIN® (clarithromycin film-coated tablets): Each oval, debossed, yellow film-coated BIAXIN® tablet contains 250 mg of clarithromycin for oral administration. Each oval, debossed, pale yellow, film-coated BIAXIN® tablet contains 500 mg of clarithromycin for oral administration.

Non-medicinal ingredients: **250 mg tablet:** cellulosic polymers, crosscarmellose sodium, D&C Yellow No. 10, magnesium stearate, povidone, propylene glycol, silicon dioxide, sorbic acid, sorbitan monooleate, pregelatinised starch, stearic acid, talc, titanium dioxide and vanillin. BIAXIN® does not contain tartrazine. **500 mg tablet:** cellulosic polymers, crosscarmellose sodium, D&C Yellow No. 10, magnesium stearate, povidone, propylene glycol, silicon dioxide, sorbic acid, sorbitan monooleate, stearic acid, talc, titanium dioxide and vanillin. BIAXIN® does not contain tartrazine. BIAXIN® (clarithromycin pediatric granules for suspension) consists of a granulation of clarithromycin and carbopol which is coated with HP-55 polymer (hydroxypropyl methylcellulose phthalate). The coated granules are mixed with a blend of inactive ingredients (sucrose, xanthan gum, silicon dioxide, potassium sorbate, citric acid, flavour, povidone (K90), castor oil, sodium chloride and saccharine). Water is added to reconstitute the suspension prior to use.

Storage Recommendations: Store tablets at controlled room temperature 15° to 30°C (59° to 86°F) in a well-closed container. Protect from light.

Store granules for suspension at controlled room temperature 15° to 30°C (59° to 86°F) in a tightly closed bottle. Protect from light.

Directions for reconstitution: **150 mL size**: 80 mL of water should be added to the granules in the bottle and shaken to yield 150 mL of reconstituted suspension. **105 mL size**: 56 mL of water should be added to the granules in the bottle and shaken to yield 105 mL of reconstituted suspension. **60 mL size**: 32 mL of water should be added to the granules in the bottle and shaken to yield 60 mL of reconstituted suspension. The reconstituted suspension must not be refrigerated. Any reconstituted unused medication should be discarded after 14 days.

AVAILABILITY OF DOSAGE FORMS: BIAXIN® (clarithromycin film-coated tablets) are supplied in HDPE bottles of 100, 250, and 500 tablets as oval, debossed, yellow, film-coated tablets containing 250 mg of clarithromycin, and HDPE bottles of 100 and 250 tablets as oval, debossed, pale yellow, film-coated tablets containing 500 mg of clarithromycin. BIAXIN® (clarithromycin pediatric granules for suspension) is supplied as a granular preparation in HDPE bottles which allow capacity for shaking. When reconstituted, the concentration of clarithromycin is 125 mg/5 mL.

Adult References: 1. Dabernat H, Delmas C, Seguy M, et al. The activity of clarithromycin and its 14-hydroxy metabolite against *Haemophilus influenzae*, determined by in-vitro and serum bactericidal tests. *J Antimicrob Chemother* 1991;27(suppl A):19-30. **2.** Mandell LA. The renaissance of the macrolides: new and changing roles in infectious diseases. *Can J Infect Dis* 1993;4(suppl A):1A-4A. **3.** Biaxin Product Monograph. Abbott Laboratories, Limited. **4.** Wettengel R, Vetter N, Waardenburg FA. Clarithromycin versus cefaclor for the treatment of mild-to-moderate acute bacterial bronchitis. *J Antimicrob Chemother* 1993;31(6):963-72. **5.** Guay DRP, Siepman N, Tanaka SK, et al. Comparative safety and efficacy of clarithromycin and 3 oral cephalosporins in the treatment of outpatients with bacterial bronchitis due to *Haemophilus influenzae*. *Drug Invest* 1993;6(1):33-41.

Pediatric References: 1. Coles SJ, Addlestone MB, Kamdar MK, et al. A comparative study of clarithromycin and amoxicillin suspensions in the treatment of pediatric patients with acute otitis media. *Infection* 1993;21(4):272-8. **2.** Aspin MM, Hoberman A, McCarty J, et al. Comparative study of the safety and efficacy of clarithromycin and amoxicillin-clavulanate in the treatment of acute otitis media in children. *J Pediatr* 1994;125(1): 136-41. **3.** Pukander JS, Jero JP, Kaprio EA, et al. Clarithromycin *vs.* amoxicillin suspensions in the treatment of pediatric patients with acute otitis media. *Pediatr Infect Dis J* 1993;12:S118-21. **4.** McCarty JM, Phillips A, Wiisanen R. Comparative safety and efficacy of clarithromycin and amoxicillin/clavulanate in the treatment of acuteotitis media in children. *Pediatr Infect Dis J* 1993;12:S122-7. **5.** Biaxin Product Monograph. Abbott Laboratories, Limited.

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MONTREAL, QUEBEC H3C 3K6

Product Monograph available on request.

PAAB

PrEFFEXOR®

VENLAFAXINE HCL TABLETS

ANTIDEPRESSANT

ACTIONS AND CLINICAL PHARMACOLOGY

Venlafaxine is a phenethylamine bicyclic derivative, chemically unrelated to tricyclic, tetracyclic or other available antidepressant agents. The mechanism of venlafaxine's antidepressant action in humans is believed to be associated with its potentiation of neurotransmitter activity in the CNS. Preclinical studies have shown that venlafaxine and its major metabolite, O-desmethylvenlafaxine (ODV), are potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. Venlafaxine and ODV have no significant affinity for muscarinic, histaminergic, or α_1-adrenergic receptors *in vitro*. Pharmacologic activity at these receptors is hypothesized to be associated with the various anticholinergic, sedative, and cardiovascular effects seen with other psychotropic drugs. Venlafaxine and ODV do not possess monoamine oxidase (MAO) inhibitory activity.

Pharmacokinetics: Venlafaxine is well absorbed, with peak plasma concentrations occurring approximately 2 hours after dosing. Venlafaxine is extensively metabolized, with O-desmethylvenlafaxine, (ODV, the only major active metabolite) peak plasma levels occurring approximately 4 hours after dosing. Following single doses of 25 to 75 mg, mean (± SD) peak plasma concentrations of venlafaxine range from 34 ± 14 to 96 ± 43 ng/mL, respectively, and are reached in 2 ± 1 hours, and mean peak ODV plasma concentrations range from 58 ± 18 to 178 ± 40 ng/mL and are reached in 4 ± 2 hours. Approximately 87% of a single dose of venlafaxine is recovered in the urine within 48 hours as either unchanged venlafaxine (5%), unconjugated ODV (30%), conjugated ODV (26%), or other minor metabolites (27%).

Multiple-Dose Pharmacokinetic Profile: Steady-state concentrations of both venlafaxine and ODV in plasma were attained after approximately 3 days of multiple dose therapy. The clearance of venlafaxine is slightly (15%) lower following multiple doses than following a single dose. Venlafaxine and ODV exhibited linear kinetics over the dose range of 75 to 450 mg total daily dose administered t.i.d. The mean ± SD steady-state plasma clearances of venlafaxine and ODV are 1.3 ± 0.6 and 0.4 ± 0.2 L/h/kg, respectively; elimination half-life is 5 ± 2 and 11 ± 2 hours, respectively. Venlafaxine and ODV renal clearances are 49 ± 27 and 94 ± 56 mL/h/kg, respectively, which correspond to 5 ± 3.0% and 25 ± 13% of an administered venlafaxine dose recovered in urine as venlafaxine and ODV, respectively. Similar steady-state volumes of distribution are exhibited for venlafaxine (7 ± 4 L/kg) and ODV (6 ± 2 L/kg). Venlafaxine and ODV are less than 35% bound to plasma proteins. Therefore, protein-binding-induced drug interactions with venlafaxine are not expected. Food has no significant effect on the absorption of venlafaxine. When equal daily doses of venlafaxine were administered either b.i.d. or t.i.d., drug exposure (AUC) and fluctuation in plasma levels were comparable.

Age and Gender: Age and sex do not significantly affect the pharmacokinetics of venlafaxine. A 20% reduction in clearance was noted for ODV in subjects over 60 years old; this was possibly caused by the decrease in renal function that typically occurs with aging. Dosage adjustment based upon age or gender is generally not necessary (See Dosage and Administration).

Hepatic Disease: In 9 patients with hepatic cirrhosis, the pharmacokinetic disposition of both venlafaxine and ODV were significantly altered. Venlafaxine elimination half-life was prolonged by about 30%, and clearance was decreased by about 50%. ODV elimination half-life was also prolonged (by about 60%) and its clearance decreased by about 30%. Three patients with more severe cirrhosis had a 90% decrease in venlafaxine clearance. **Dosage adjustment is necessary in patients with liver disease (See Dosage and Administration).**

Renal Disease: In patients with moderate to severe impairment of renal function (GFR = 10-70 mL/min.), venlafaxine elimination half-life was prolonged by 50%, and clearance was deceased by about 24%. ODV elimination half-life was prolonged by about 40%, but clearance was unchanged. In dialysis patients, venlafaxine elimination half-life was prolonged by about 180% and clearance was decreased by about 56%. **Dosage adjustment is necessary in patients with renal disease (See Dosage and Administration).**

INDICATIONS AND CLINICAL USE

EFFEXOR (venlafaxine) is indicated for the symptomatic relief of depressive illness. The effectiveness of EFFEXOR in long-term use (i.e., for more than 4 to 6 weeks) has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use EFFEXOR for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

EFFEXOR (venlafaxine) is contraindicated in patients with known hypersensitivity to venlafaxine or to any of the components of the formulation.

Monoamine Oxidase Inhibitors (MAOI's): There have been reports of serious, sometimes fatal reactions in patients receiving antidepressants with pharmacological properties similar to those of EFFEXOR in combination with a MAOI. Therefore, EFFEXOR should not be used in combination with MAOI's or within two weeks of terminating treatment with MAOI's. Treatment with MAOI's should not be started until two weeks after discontinuation of EFFEXOR therapy.

WARNINGS

Sustained Hypertension: Treatment with EFFEXOR was associated with modest but sustained increases in blood pressure during premarketing studies. Sustained hypertension, defined as treatment-emergent supine diastolic blood pressure (SDBP) ≥ 90 mm Hg **and** ≥ 10 mm Hg above baseline for 3 consecutive visits, showed the following incidence and dose-relationship:

Probability of Sustained Elevation in SDBP
(Pool of Premarketing Studies with EFFEXOR)

Treatment Group	Incidence of Sustained Elevation in SDBP
Venlafaxine	
<100 mg/day	3%
101-200 mg/day	5%
201-300 mg/day	7%
>300 mg/day	13%
Placebo	2%

An analysis of the blood pressure increases in patients with sustained hypertension and in the 19 patients who were discontinued from treatment because of hypertension (<1% of total venlafaxine-treated group) showed that most of the blood pressure increases were in the range of 10 to 15 mm Hg, SDBP. Since in individual patients sustained increases of this magnitude could have adverse consequences, it is recommended that patients receiving venlafaxine have their blood pressure monitored regularly. For patients who experience a sustained increase in blood pressure during treatment with venlafaxine, either a dose reduction or discontinuation of venlafaxine should be considered.

PRECAUTIONS

General

Suicide: The possibility of a suicide attempt in seriously depressed patients is inherent to the illness and may persist until significant remission occurs. Close supervision of high-risk patients should accompany initial drug therapy, and consideration should be given to the need for hospitalization. In order to reduce the risk of overdose, prescriptions for EFFEXOR should be written for the smallest quantity of tablets consistent with good patient management.

Seizures: During premarketing testing, seizures were reported in 8 out of 3082 venlafaxine-treated patients (0.26%). In 5 of the 8 cases, patients were receiving doses of 150 mg/day or less. However, patients with a history of convulsive disorders were excluded from most of these studies. EFFEXOR should be used cautiously in patients with a history of seizures, and should be promptly discontinued in any patient who develops seizures.

Activation of Mania/Hypomania: During Phase II and III trials, mania or hypomania occurred in 0.5% of venlafaxine-treated patients. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorder who were treated with other marketed antidepressants. As with all antidepressants, EFFEXOR should be used cautiously in patients with a history of mania.

Use in Patients with Concomitant Illness: Clinical experience with venlafaxine in patients with concomitant systemic illness is limited. Caution is advised in administering venlafaxine to patients with diseases or conditions that could affect hemodynamic responses or metabolism. Patients should be questioned about any prescription or "over the counter drugs" that they are taking, or planning to take, since there is a potential for interactions.

- **Cardiac Disease**
  Venlafaxine has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from many clinical studies during the product's clinical trials. Evaluation of the electrocardiograms for 769 patients who received venlafaxine in 4- to 6-week double-blind trials showed that the incidence of trial-emergent conduction abnormalities did not differ from that with placebo. The mean heart rate was increased by about 4 beats per minute during treatment. Venlafaxine treatment has been associated with sustained hypertension **(see WARNINGS.)**
- **Hepatic and Renal Disease**
  In patients with hepatic or renal disease the pharmacokinetic disposition of both venlafaxine and ODV are significantly altered. **Dosage adjustment is necessary in these patients (See Dosage and Administration).**

Interference With Cognitive and Motor Performance: Any psychoactive drug may impair judgement, thinking or motor skills. Therefore, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that the drug treatment does not affect them adversely.

Use in Pregnancy, Labour and Delivery: There are no adequate and well controlled studies with venlafaxine in pregnant women. Therefore, venlafaxine should only be used during pregnancy if clearly needed.

Use in Nursing Mothers: It is not known whether venlafaxine or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, lactating women should not nurse their infants while receiving venlafaxine.

Paediatric Use: Safety and efficacy in children below the age of 18 have not been established.

Use in the Elderly: Of the 2,897 patients in Phase II and III trials, 357 (12%) were 65 years of age or older. No overall differences in effectiveness and safety were observed between these patients and younger patients. However, greater sensitivity of some older individuals cannot be ruled out.

Discontinuation Symptoms: While the discontinuation effects of EFFEXOR have not been systematically evaluated in controlled clinical trials, a retrospective survey of new events occurring during taper or following discontinuation revealed the following six events that occurred at an incidence of at least 5%, and for which the incidence for EFFEXOR was at least twice the placebo incidence: asthenia, dizziness, headache, insomnia, nausea and nervousness. Therefore, it is recommended that the dosage be tapered gradually and the patient monitored **(See Dosage and Administration).**

Drug Interactions: As with all drugs, the potential for interaction by a variety of mechanisms is a possibility.

- ***Lithium***
  The steady-state pharmacokinetics of venlafaxine administered as 50 mg every 8 hours was not affected when a single 600 mg oral dose of lithium was administered to 12 healthy male subjects. Venlafaxine had no effect on the pharmacokinetics of lithium. It should be noted that the venlafaxine dose was in the low end of the therapeutic dosage, as was the single lithium dose. **The potential interaction of venlafaxine and lithium in clinical practice is unknown.**
- ***Diazepam***
  The steady-state pharmacokinetics of venlafaxine administered as 50 mg every 8 hours was not affected when a single 10 mg oral dose of diazepam was administered to 18 healthy male subjects. Venlafaxine had no effect on the pharmacokinetics of diazepam or its active metabolite, desmethyldiazepam. It should be noted that the venlafaxine dose was in the low end of the therapeutic dosage, as was the single diazepam dose. **The potential interaction of venlafaxine and diazepam in clinical practice is unknown.**
- ***Cimetidine***
  Concomitant administration of cimetidine and venlafaxine in a steady-state study for both drugs in 18 healthy male subjects resulted in inhibition of first-pass metabolism of venlafaxine. The oral clearance of venlafaxine was reduced by about 43%, and the exposure (AUC) and maximum concentration (Cmax) of the drug were increased by about 60%. However, there was no effect on the pharmacokinetics of ODV. The overall pharmacological activity of venlafaxine plus ODV is expected to rise only slightly, and no dosage adjustment should be necessary for most subjects.
  However, for patients with pre-existing hypertension, for elderly patients and for patients with hepatic or renal dysfunction, the interaction associated with the concomitant use of cimetidine and venlafaxine is not known and potentially could be more pronounced. Therefore, caution is advised in these patients.
- ***Other CNS-Active Drugs***
  The risk of using venlafaxine in combination with other CNS-active drugs (including alcohol) has not been systematically evaluated. Consequently, caution is advised if the concomitant administration of venlafaxine and such drugs is required.

Electroconvulsive Therapy: There are no clinical data on the use of electroconvulsive therapy combined with EFFEXOR treatment.

Cytochrome $P_{450}IID_6$: Venlafaxine is metabolized to its active metabolite, ODV, by cytochrome $P_{450}IID_6$. Therefore, the potential exists for a drug interaction between EFFEXOR and drugs that inhibit cytochrome $P_{450}IID_6$ metabolism. Venlafaxine is a relatively weak inhibitor of cytochrome $P_{450}IID_6$, however, the clinical significance of this finding is unknown.

Drug Abuse and Dependence

Physical and Psychological Dependence: *In vitro* studies revealed that venlafaxine has virtually no affinity for opiate, benzodiazepine, phencyclidine (PCP), or N-methyl-D-aspartic acid (NMDA) receptors. It has no significant CNS stimulant activity in rodents. In primate drug discrimination studies, venlafaxine showed no significant stimulant or depressant abuse liability.

While EFFEXOR has not been systematically studied in clinical trials for its potential for abuse, there was no indication of drug-seeking behaviour in the clinical trials. However, it is not possible to predict on the basis of premarketing experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of venlafaxine (e.g., development of tolerance, incrementation of dose, drug-seeking behaviour).

ADVERSE REACTIONS

Commonly Observed Adverse Reactions: The most commonly observed adverse events associated with the use of EFFEXOR (incidence of 5% or greater) and not seen at an equivalent incidence among placebo-treated patients (i.e., incidence for EFFEXOR at least twice that for placebo), derived from the 1% incidence Table 2, were asthenia, sweating, nausea, constipation, anorexia, vomiting, somnolence, dry mouth, dizziness, nervousness, anxiety, tremor, blurred vision, and abnormal ejaculation/orgasm and impotence in men.

Adverse Reactions Associated with Discontinuation of Treatment: Nineteen percent (537/2897) of venlafaxine-treated patients in Phase II and III depression studies discontinued treatment due to an adverse reaction (Table 1). The more common events (≥1%) associated with discontinuation of treatment and considered to be drug-related (i.e., those events associated with dropout at a rate approximately twice or greater for venlafaxine compared to placebo) included:

TABLE 1: ADVERSE REACTIONS ASSOCIATED WITH DISCONTINUATION OF TREATMENT

CNS	Venlafaxine	Placebo
Somnolence	3%	1%
Insomnia	3%	1%
Dizziness	3%	–
Nervousness	2%	–
Dry Mouth	2%	–
Anxiety	2%	1%
Gastrointestinal		
Nausea	6%	1%
Urogenital		
Abnormal Ejaculation*	3%	–
Other		
Headache	3%	1%
Asthenia	2%	–
Sweating	2%	–

*: percentages based on the number of males. –: Less than 1%

Incidence in Controlled Trials: The table that follows enumerates adverse events that occurred at an incidence of 1% or more, and were more frequent than in the placebo group, among venlafaxine-treated patients who participated in 4- to 8-week placebo-controlled trials in which patients were administered doses in the range of 75 to 375 mg/day. Reported adverse events were classified using a standard COSTART-based dictionary terminology.

TABLE 2: TREATMENT-EMERGENT ADVERSE EXPERIENCE INCIDENCE IN 4-TO 8-WEEK PLACEBO-CONTROLLED CLINICAL TRAILS (PERCENTAGE)[1]

Body System	Preferred Term	Effexor (n=1033)	Placebo (n=609)
Body as a whole	Headache	25	24
	Asthenia	12	6
	Infection	6	5
	Chills	3	-
	Chest Pain	2	1
	Trauma	2	1
Cardiovascular	Vasodilatation	4	3
	Increased blood pressure/ hypertension	2	-
	Tachycardia	2	-
	Postural hypotension	1	-
Dermatological	Sweating	12	3
	Rash	3	2
	Pruritus	1	-
Gastrointestinal	Nausea	37	11
	Constipation	15	7
	Anorexia	11	2
	Diarrhoea	8	7
	Vomiting	6	2
	Dyspepsia	5	4
	Flatulence	3	2
Metabolic	Weight loss	1	-
Nervous	Somnolence	23	9
	Dry mouth	22	11
	Dizziness	19	7
	Insomnia	18	10
	Nervousness	13	6
	Anxiety	6	3
	Tremor	5	1
	Abnormal Dreams	4	3
	Hypertonia	3	2
	Paraesthesia	3	2
	Libido decreased	2	-
	Agitation	2	-
	Confusion	2	1
	Thinking abnormal	2	1
	Depersonalization	1	-
	Depression	1	-
	Urinary retention	1	-
	Twitching	1	-
Respiration	Yawn	3	-
Special Senses	Blurred vision	6	2
	Taste perversion	2	-
	Tinnitus	2	-
	Mydriasis	2	-
Urogenital System	Abnormal ejaculation/ orgasm	12[2]	-[2]
	Impotence	6[2]	-[2]
	Urinary frequency	3	2
	Urination impaired	2	-
	Orgasm disturbance	2[3]	-[3]
	Menstrual disorder	1[3]	-[3]

1 Events reported by at least 1% of patients treated with Effexor are included, and are rounded to the nearest %. Events for which the Effexor incidence was equal to or less than placebo are not listed in the table, but included the following: abdominal pain, pain, back pain, flu syndrome, fever, palpitation, increased appetite, myalgia, arthralgia, amnesia, hypaesthesia, rhinitis, pharyngitis, sinusitis cough increased, urinary tract infection, and dysmenorrhoea[3]. - Incidence less than 1%

2 Incidence based on number of male patients.

3 Incidence based on number of female patients

Dose Dependency of Adverse Events: A comparison of adverse event rates in a fixed-dose study comparing Effexor 75, 225, and 375 mg/day with placebo revealed a dose dependency for some of the more common adverse events associated with Effexor use, as shown in the table that follows. The rule for including events was to enumerate those that occurred at an incidence of 5% or more for at least one of the venlafaxine groups and for which the incidence was at least twice the placebo incidence for at least one Effexor group. Tests for potential dose relationships for these events (Cochran-Armitage Test, with a criterion of exact 2-sided p-value ≤ 0.05) suggested a dose-dependency for several adverse events in this list, including chills, hypertension, anorexia, nausea, agitation, dizziness, somnolence, tremor, yawning, sweating, and abnormal ejaculation.

TABLE 3: TREATMENT-EMERGENT ADVERSE EXPERIENCE INCIDENCE IN A DOSE COMPARISON TRIAL

Body System/ Preferred Term	Effexor (mg/day) Placebo (n=92)	75 (n=89)	225 (n=89)	375 (n=88)
Body as whole				
Abdominal pain	3.3%	3.4%	2.2%	8.0%
Asthenia	3.3%	16.9%	14.6%	14.8%
Chills	1.1%	2.2%	5.6%	6.8%
Infection	2.2%	2.2%	5.6%	2.3%
Cardiovascular				
Hypertension	1.1%	1.1%	2.2%	4.5%
Vasodilatation	0.0%	4.5%	5.6%	2.3%
Digestive System				
Anorexia	2.2%	14.6%	13.5%	17.0%
Dyspepsia	2.2%	6.7%	6.7%	4.5%
Nausea	14.1%	32.6%	38.2%	58.0%
Vomiting	1.1%	7.9%	3.4%	6.8%
Nervous				
Agitation	0.0%	1.1%	2.2%	4.5%
Anxiety	4.3%	11.2%	4.5%	2.3%
Dizziness	4.3%	19.1%	22.5%	23.9%
Insomnia	9.8%	22.5%	20.2%	13.6%
Libido decreased	1.1%	2.2%	1.1%	5.7%
Nervousness	4.3%	21.3%	13.5%	12.5%
Somnolence	4.3%	16.9%	18.0%	26.1%
Tremor	0.0%	1.1%	2.2%	10.2%
Respiratory				
Yawn	0.0%	4.5%	5.6%	8.0%
Skin and Appendages				
Sweating	5.4%	6.7%	12.4%	19.3%
Special senses				
Abnormality of accommodation	0.0%	9.1%	7.9%	5.6%
Urogenital System				
Abnormal ejaculation/ orgasm	0.0%	4.5%	2.2%	12.5%
Impotence	0.0% (n=63)	5.8% (n=52)	2.1% (n=48)	3.6% (n=56)

Adaptation to Certain Adverse Events: Over a 6-week period, there was evidence of adaptation to some adverse events with continued therapy (e.g., dizziness and nausea), but less to other effects (e.g., abnormal ejaculation and dry mouth).

Vital Sign Changes: Effexor treatment (averaged over all dose groups) in clinical trials was associated with a mean increase in pulse rate of approximately 3 beats per minute, compared to no change for placebo. It was associated with mean increases in diastolic blood pressure ranging from 0.7 to 2.5 mm Hg averaged over all dose groups, compared to mean decreases ranging from 0.9 to 3.8 mm Hg for placebo. However, there is a dose dependency for blood pressure increase (see WARNINGS).

Laboratory Changes: Of the serum chemistry and haematology parameters monitored during clinical trials with Effexor, a statistically significant difference with placebo was seen only for serum cholesterol, i.e., patients treated with Effexor had mean increases from baseline of 3 mg/dL, a change of unknown clinical significance.

ECG Changes: In an analysis of ECGs obtained in 769 patients treated with Effexor and 450 patients treated with placebo in controlled clinical trials, the only statistically significant difference observed was for heart rate, i.e., a mean increase from baseline of 4 beats per minute for Effexor.

Other Events Observed During the Premarketing Evaluation of Venlafaxine: During its premarketing assessment, multiple doses of Effexor were administered to 2,181 patients in phase II and III studies. The conditions and duration of exposure of Effexor varied greatly, and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, fixed-dose and titration studies. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories. In the tabulations that follow, reported adverse events were classified using a standard COSTART-based dictionary terminology. The frequencies presented, therefore, represent the proportion of the 2,181 patients exposed to multiple doses of Effexor who experienced an event of the type cited on at least one occasion while receiving Effexor. All reported events are included except those already listed in Table 2 and those events for which a drug cause was remote. If the COSTART term for an event was so general as to be uninformative, it was replaced with a more informative term. It is important to emphasize that, although the events reported occurred during treatment with Effexor, they were not necessarily caused by it. Events are further classified by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from placebo controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. The frequent adverse events have been provided below.

Body as a whole–accidental injury, malaise, neck pain. **Cardiovascular system**–migraine. **Digestive system**–dysphagia, eructation. **Haemic and lymphatic system**–ecchymosis. **Metabolic and nutritional**–peripheral edema, weight gain. **Nervous system**–emotional lability, trismus, vertigo. **Respiratory system**–bronchitis, dyspnea. **Special senses**–abnormal vision, ear pain. **Urogenital system**–anorgasmia, dysuria, haematuria, metrorrhagia*, urination impaired, vaginitis*.

*Based on the number of male or female patients as appropriate.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Human Experience: There were 14 reports of acute overdose with Effexor (venlafaxine hydrochloride), either alone or in combination with other drugs and/or alcohol, among the patients included in the premarketing evaluation. The majority of the reports involved ingestions in which the total dose of Effexor taken was estimated to be no more than several-fold higher than the usual therapeutic dose. The 3 patients who took the highest doses were estimated to have ingested approximately 6.75 g, 2.75 g and 2.5 g. The resultant peak plasma levels of venlafaxine for the latter 2 patients were 6.24 and 2.35 µg/mL, respectively, and the peak plasma levels of O-desmethylvenlafaxine were 3.37 and 1.30 µg/mL, respectively. Plasma venlafaxine levels were not obtained for the patient who ingested 6.75 g of venlafaxine. All 14 patients recovered without sequelae. Most patients reported no symptoms. Among the remaining patients, somnolence was the most commonly reported symptom. The patient who ingested 2.75 g of venlafaxine was observed to have 2 generalized convulsions and a prolongation of QTc to 500 msec, compared with 405 msec at baseline. Mild sinus tachycardia was reported in 2 of the other patients.

Overdosage Management: Treatment should consist of those general measures employed in the management of overdosage with any antidepressant. Ensure an adequate airway, oxygenation, and ventilation. Monitoring of cardiac rhythm and vital signs is recommended. General supportive and symptomatic measures are also recommended. Use of activated charcoal, induction of emesis, or gastric lavage should be considered. Due to the large volume of distribution of venlafaxine hydrochloride, forced diuresis, dialysis, haemoperfusion and exchange transfusion are unlikely to be of benefit. No specific antidotes for Effexor are known. In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control centre on the treatment of any overdose.

DOSAGE AND ADMINISTRATION

Adults: The recommended treatment dose is 75 mg per day, administered in two or three divided doses, taken with food. If the expected clinical improvement does not occur after a few weeks, a gradual dose increase to 150 mg/day may be considered. If needed, the dose may be further increased up to 225 mg/day. Increments of up to 75 mg/day should be made at intervals of no less than 4 days. In outpatient settings there was no evidence of the usefulness of doses greater than 225 mg/day for moderately depressed patients. More severely depressed inpatients have responded to higher doses, between 350 and 375 mg/day, given in three divided doses.

Maximum: The maximum dose recommended is 375 mg per day (in an inpatient setting).

Patients With Hepatic Impairment: Given the decrease in clearance and increase in elimination half-life for both venlafaxine and ODV that is observed in patients with hepatic cirrhosis compared to normal subjects (see CLINICAL PHARMACOLOGY), it is recommended that the total daily dose be reduced by about 50% in patients with moderate hepatic impairment. Since there was much individual variability in clearance between patients with cirrhosis, it may be necessary to reduce the dose even more than 50%, and individualization of dosing may be desirable in some patients.

Patients with Renal Impairment: Given the decrease in clearance for venlafaxine and increase in elimination half-life for both venlafaxine and ODV that is observed in patients with renal impairment (GFR = 10-70 mL/min) compared to normals (see CLINICAL PHARMACOLOGY), it is recommended that the total daily dose be decreased by 25% in patients with mild to moderate renal impairment. It is recommended that the total daily dose be reduced by 50% and the dose be withheld until the dialysis treatment is completed (4 hrs) in patients undergoing haemodialysis. Since there was so much individual variability in clearance between patients with renal impairment, individualization of dosing may be desirable in some patients.

Elderly Patients: No dose adjustment is recommended for elderly patients on the basis of their age. As with any antidepressant, however, caution should be exercised in treating the elderly. When individualizing the dosage, extra care should be taken when increasing the dose.

Discontinuing Venlafaxine: When venlafaxine therapy that has been administered for more than 1 week is stopped, it is generally recommended that the dose be tapered gradually to minimize the risk of discontinuation symptoms. Patients who have received venlafaxine for 6 weeks or more should have their dose tapered gradually over a 2-week period.

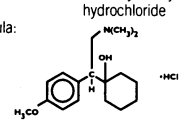
PHARMACEUTICAL INFORMATION

Drug Substance:

Proper Name: Venlafaxine Hydrochloride

Chemical Name: (R/S)-1-[2-(dimethylamino)-1-(4-methoxyphenyl) ethyl] cyclohexanol hydrochloride; or (R/S)-1[α[(dimethylamino)methyl]-p-methoxy-benzyl]cyclohexanol hydrochloride

Structural Formula:



Molecular Weight:	313.87
Physical Form:	White, crystalline solid
Solubility:	
Water:	540, 542, 501 and 21.6 mg/mL at pH 1.0, 5.38, 7.09 and 7.97.
Ethanol:	91.7 mg/mL
Propylene Glycol:	200 mg/mL
Glycerin:	115 mg/mL
pKa value:	9.4

Composition:

Medicinal Ingredients	Non-medicinal Ingredients:
Venlafaxine Hydrochloride	Microcrystalline Cellulose NF
	Lactose NF Hydrous
	Cosmetic Brown Iron Oxide
	Ferric Oxide NF Yellow
	Sodium Starch Glycolate NF
	Magnesium Stearate NF

Stability and Storage Recommendations:

Store at room temperature (15-30° C), in a dry place.

AVAILABILITY OF DOSAGE FORMS

EFFEXOR® is available, in bottles of 100 tablets, in the following tablet strengths:

(Potency is expressed in terms of venlafaxine base.)

37.5 mg Shield-shaped, peach-coloured compressed tablet, with a score, with "Wyeth-Ayerst logo" on one side and "37.5" on the other side.

75 mg Shield-shaped, peach-coloured compressed tablet, with a score, with "Wyeth-Ayerst logo" on one side and 75 on the other side.

References: 1. EFFEXOR Product Monograph, Wyeth-Ayerst Canada Inc. **2.** Preskorn SH, Burke M. Somatic therapy for major depressive disorder: selection of an antidepressant. *J Clin Psychiatry* 1992;53:(9, suppl).5-18. **3.** Richelson E. Synaptic pharmacology of antidepressants: an update. *McLean Hosp* J 1988;13:67-88. **4.** Clerc GE., Ruimy P., Verdeau-Paillès J. A double-blind comparison of venlafaxine and fluoxetine in patients hospitalized for major depression and melancholia. *Int Clin Psychopharm* 1994;9:139-143. **5.** Feighner JP. The role of venlafaxine in rational antidepressant therapy. *J Clin Psychiatry* 1994;55(9, suppl A):62-68. *Prozac® (fluoxetine HCl) is a registered trademark of Eli Lilly Canada Inc. Product Monograph available on request. PAAB

RELAFEN™
NABUMETONE

500 mg ORAL TABLETS

THERAPEUTIC CLASSIFICATION

Nonsteroidal anti-inflammatory agent (NSAID)

ACTION AND CLINICAL PHARMACOLOGY: Nabumetone is a non-acidic, nonsteroidal anti-inflammatory drug (NSAID) with a naphthylalkanone structure which is virtually insoluble in water. It exhibits anti-inflammatory, analgesic and antipyretic properties in pharmacologic studies. As with the acidic NSAIDs, its mode of action is not known. However, the ability to inhibit prostaglandin synthesis may be involved in the anti-inflammatory effect. Nabumetone, as the parent compound, is a pro-drug which undergoes rapid hepatic biotransformation to its principal active metabolite, 6-methoxy-2-naphthylacetic acid (6-MNA), a potent inhibitor of prostaglandin biosynthesis.

Relafen (nabumetone) was compared to ASA in inducing gastrointestinal blood loss. Food intake was not monitored. Studies utilizing ^{51}Cr-tagged red blood cells in healthy males showed no difference in fecal blood loss after three or four weeks' therapy of Relafen 1000 mg or 2000 mg daily when compared to either placebo-treated or non-treated subjects. In contrast, ASA 3600 mg daily produced an increase in fecal blood loss when compared to the Relafen-, placebo- or non-treated subjects.

In one-week repeat dose studies in healthy volunteers, Relafen 1000 mg daily had little effect on collagen-induced platelet aggregation and no effect on bleeding time.

Pharmacokinetics: After oral administration, approximately 80% of a radio-labelled dose of nabumetone is found in the urine, indicating that nabumetone is well absorbed from the gastrointestinal tract. Nabumetone itself is not quantifiable in the plasma because, after absorption, it undergoes rapid biotransformation to the principal active metabolite, 6-MNA. Approximately 35% of a 1000 mg dose of nabumetone is converted to 6-MNA and 50% is converted into unidentified metabolites which are subsequently excreted in the urine.

Following oral administration, peak plasma levels of 6-MNA occur between 2.5 and 4 hours (range 1 to 12 hours). Preliminary *in vivo* and *in vitro* studies suggest that unlike other NSAIDs, there is no evidence of enterohepatic recirculation of the active metabolite. Steady-state is generally achieved between 3 and 6 days and the elimination half life is variable from 23 (±3.7) hours in young healthy patients to 30 (±8.1) hours in the elderly.

The active metabolite penetrates into the synovial fluids at measurable sustained levels in osteoarthritis and rheumatoid arthritis patients. There is wide inter-individual variation in plasma concentrations of 6-MNA. A correlation between plasma 6-MNA levels and efficacy has not been established.

6-MNA is more than 99% bound to plasma proteins. The free fraction is dependent on total concentration of 6-MNA and is proportional to dose over the range of 1000 to 2000 mg. It is 0.2% to 0.3% at concentrations typically achieved following administration of nabumetone 1000 mg and is approximately 0.6% to 0.8% of the total concentrations at steady-state following daily administration of 2000 mg.

Table 1: Mean pharmacokinetic parameters of nabumetone active metabolite (6-MNA) at steady-state following oral administration of 1000 mg or 2000 mg doses of nabumetone

Abbreviations (units)	Young Adults Mean ± SD 1000 mg n=31	Young Adults Mean ± SD 2000 mg n=12	Elderly Mean ± SD 1000 mg n=27
t_{max} (hours)*	3.0 (1.0 to 12.0)	2.5 (1.0 to 8.0)	4.0 (1.0 to 10.0)
$t_{1/2}$ (hours)	22.5 ± 3.7	26.2 ± 3.7	29.8 ± 8.1
Cl_{ss}/F (mL/min)	26.1 ± 17.3	21.0 ± 4.0	18.6 ± 13.4
Vd_{ss}/F(L)	55.4 ± 26.4	53.4 ± 11.3	50.2 ± 25.3

* t_{max} is reported as median (range) values.

Concomitant administration of an aluminum-containing antacid had no significant effect on the bioavailability of the active metabolite of nabumetone. When administered with food or milk, there is more rapid absorption; however, the total amount of 6-MNA in the plasma is unchanged.

Elderly: Steady state-plasma concentrations in elderly patients were generally higher than in young healthy subjects (See Table 1 for summary of pharmacokinetic parameters of 6-MNA).

Renal Insufficiency: In studies of patients with renal insufficiency, the mean terminal half life of 6-MNA was increased in patients with severe renal dysfunction (creatinine clearance < 30 mL/min/1.73m²). In patients undergoing hemodialysis, steady state plasma concentrations of the active metabolite were similar to those observed in healthy subjects. Due to extensive protein binding, 6-MNA is not dialyzable.

Hepatic Impairment: Data in patients with severe hepatic impairment are limited. Biotransformation of nabumetone to 6-MNA and the further metabolism of 6-MNA to inactive metabolites is dependent on hepatic function and could be reduced in patients with severe hepatic impairment (history of or biopsy-proven cirrhosis).

INDICATIONS AND CLINICAL USE: Relafen (nabumetone) is indicated for acute and chronic relief of the signs and symptoms of rheumatoid arthritis and osteoarthritis.

CONTRAINDICATIONS: Relafen (nabumetone) is contraindicated in patients who have previously exhibited hypersensitivity to it.

Relafen should not be given to patients in whom ASA or other NSAIDs induce asthma, urticaria or other allergic type reactions. Fatal anaphylactoid reactions have occurred in such individuals.

WARNINGS: *Risk of G.I. Ulceration, Bleeding and Perforation with NSAID Therapy:* Peptic ulceration, perforation and gastrointestinal bleeding, sometimes severe and occasionally fatal have been reported during therapy with nonsteroidal anti-inflammatory drugs (NSAIDs) including Relafen.

Relafen should be given under close medical supervision to patients prone to gastrointestinal irritation particularly those with a history of peptic ulcer, diverticulosis or other inflammatory disease of the gastrointestinal tract. In these cases the physician must weigh the benefits of treatment against the possible hazards.

Patients taking any NSAID including this drug should be instructed to contact a physician immediately if they experience symptoms or signs suggestive of peptic ulceration or gastrointestinal bleeding. These reactions can occur without warning symptoms or signs and at any time during the treatment.

Elderly, frail and debilitated patients appear to be at higher risk from a variety of adverse reactions from nonsteroidal anti-inflammatory drugs (NSAIDs). However, data from clinical studies with Relafen have indicated that there were no overall differences in efficacy or safety between older patients and younger ones. As with other NSAIDs, the lowest dose should be sought for each patient. Therefore, after observing the response to initial therapy, the dose should be adjusted to meet individual patients' requirements. See "Precautions" for further advice.

Use in Pregnancy and Lactation: As the safety and efficacy of Relafen (nabumetone) in human pregnancy and lactation have not been established, its use is therefore not recommended.

Teratogenic effects were not observed in rats or rabbits. Postnatal development was not affected even though the active metabolite of nabumetone (6-MNA) is found in the milk of lactating rats. Nabumetone and/or its active metabolites have been shown to cross the placental barrier of rats.

Children: Relafen is not recommended for use in children because the safety and efficacy in children have not been established.

PRECAUTIONS: *Gastrointestinal:* If peptic ulceration is suspected or confirmed, or if gastrointestinal bleeding or perforation occurs, Relafen should be discontinued, and appropriate treatment instituted and th patient closely monitored.

There is no definitive evidence that the concomitant administration of histamine H_2 receptor antagonists an antacids will either prevent the occurrence of gastrointestinal side effects or allow continuation of Relafen therapy when and if these adverse reactions occur.

Hepatic Impairment: As with other NSAIDs, borderline elevations of one or more liver tests may occur. Th abnormalities may progress, may remain essentially unchanged, or may be transient with continued therap A patient with symptoms and/or signs suggesting liver dysfunction, or in whom an abnormal liver test has occurred, should be evaluated for evidence of the development of a more severe hepatic reaction while on therapy with this drug.

Severe hepatic reactions, including jaundice and cases of fatal hepatitis have been reported with other NSAIDs. Although such reactions are rare, if abnormal liver tests persist or worsen, if clinical signs and symptoms consistent with liver disease develop, or if systemic manifestations occur (e.g. eosinophilia, rash etc.), this drug should be discontinued.

During long-term therapy, liver function tests should be monitored periodically. If this drug is to be used in presence of impaired liver function, it must be done under strict observation.

Renal Impairment: As with other nonsteroidal anti-inflammatory drugs, long-term administration of nabume to animals has resulted in renal papillary necrosis and other abnormal renal pathology. In humans, there h been reports of acute interstitial nephritis with hematuria, proteinuria, and occasionally nephrotic syndrome A second form of renal toxicity has been seen in patients with prerenal conditions leading to the reduction renal blood flow or blood volume, where the renal prostaglandins have a supportive role in the maintenanc renal perfusion. In these patients, administration of a nonsteroidal anti-inflammatory drug may cause a do dependent reduction in prostaglandin formation and may precipitate overt renal decompensation. Patients greatest risk of this reaction are those with impaired renal function, heart failure, liver dysfunction, those ta diuretics, and the elderly. Discontinuation of nonsteroidal anti-inflammatory therapy is usually followed by recovery to the pre-treatment state.

Relafen and its metabolites are eliminated primarily by the kidneys, therefore the drug should be used with great caution in patients with impaired renal function. Although studies have shown that no adjustment of Relafen dosage is generally necessary in patients with renal insufficiency, as with other NSAIDs, patients v severely impaired renal function should be monitored more closely than patients with normal renal functior During long-term therapy, kidney function should be monitored periodically.

Elderly: Use in the elderly and debilitated patient should be monitored more closely as NSAID use in this population is known to be associated with a higher risk of adverse events. Data from controlled clinical stu (where 24% of 1677 patients were ≥ 65 years of age) and UK post-marketing studies with Relafen (where of 10,800 patients were ≥ 65 years of age) indicate that there were no differences in efficacy or safety betv older and younger patients.

Fluid & Electrolyte Balance: Fluid retention and edema have been observed in patients treated with Relafe Therefore, as with many other NSAIDs, the possibility of precipitating congestive heart failure in elderly patients or those with compromised cardiac function should be borne in mind. Relafen should be used wit caution in patients with heart failure, hypertension or other conditions predisposing to fluid retention.

With NSAID treatment, there is a potential risk of hyperkalemia particularly in patients with conditions such diabetes mellitus or renal failure; elderly patients; or in patients receiving concomitant therapy with beta-adrenergic blockers, angiotensin converting enzyme inhibitors or some diuretics. Serum electrolytes shou monitored periodically during long-term therapy, especially in those patients at risk.

Hematology: Drugs inhibiting prostaglandin biosynthesis do interfere with platelet function to some degree therefore, patients who may be adversely affected by such an action should be carefully observed when Relafen is administered. Blood dyscrasias associated with the use of NSAIDs are rare, but could have sev consequences.

Hypersensitivity: As with other NSAIDs, allergic reactions may occur. Manifestations of allergic reactions include urticaria, dyspnea, and in rare instances anaphylaxis, or severe skin reactions such as Stevens-Johnson syndrome.

Infection: In common with other anti-inflammatory drugs, Relafen may mask the usual signs of infection.

Ophthalmology: Blurred and/or diminished vision has been reported with the use of Relafen and other NSAIDs. If such symptoms develop this drug should be discontinued and an ophthalmologic examination performed; ophthalmic examination should be carried out at periodic intervals in any patients receiving this drug for an extended period of time.

Occupational Hazards: – Dizziness or other disturbances of the central nervous system may occur follow therapy with Relafen. Patients experiencing these symptoms should be cautioned against driving or opera machinery.

Drug Interactions: – In vitro studies have shown that, because of its affinity for protein, the active metabo of nabumetone may displace other protein-bound drugs such as sulfonylureas, tolbutamide, chlorpropamic and warfarin, from their binding site. Although clinical pharmacology studies demonstrated no significant r interaction between warfarin and Relafen, concomitant administration of Relafen and warfarin or other high protein-bound drugs should be undertaken with caution.

Digoxin levels should be monitored, and if necessary, a dosage adjustment made when administered concomitantly with Relafen. Nonsteroidal anti-inflammatory drugs have also been reported to increase ste state plasma lithium concentrations. It is recommended that these concentrations be monitored when initiating, adjusting or discontinuing Relafen treatment. Rare cases of fatal renal toxicity have occurred wh methotrexate and NSAIDs are given concomitantly.

Concomitant administration of an aluminum-containing antacid had no significant effect on the bioavailabili 6-MNA. When administered with food or milk, there is more rapid absorption; however, the total amount o MNA in the plasma is unchanged.

Concomitant administration of acetaminophen, ASA or cimetidine did not affect the bioavailability of the principal circulating metabolite in volunteer subjects.

In controlled rheumatoid arthritis trials, Relafen has been used in combination with gold, d-penicillamine, a corticosteroids. There was no evidence of untoward effects associated with their concurrent administratior

ADVERSE REACTIONS: The most common adverse reactions encountered with NSAIDs are gastrointest of which peptic ulcer, with or without bleeding, is the most severe. Fatalities have occurred on occasion particularly in the elderly.

Adverse reaction information was derived from blinded-controlled and open-labelled clinical trials and from worldwide marketing experience. Over 6,000 patients have been treated with Relafen (nabumetone) in cli trials, and over 49,000 patients included in post-marketing surveillance studies. Relafen has been prescril extensively in those countries where the drug has received registration clearance.

In large scale post-marketing studies the adverse event profile was highly consistent with the profile seen clinical trials of Relafen. The pattern of adverse events remained similar in patients treated with Relafen f several years, similar in patients taking 1-2 g doses, and was similar in patients aged <65 or ≥65 years.

In the description below, information on adverse experiences observed in U.S. clinical studies is presentec the 1,677 patients who received Relafen during U.S. clinical trials, 1,524 were treated for at least one mon 1,327 for at least three months, 929 for at least a year and 750 for at least two years. Over 300 patients h been treated for five years or longer.

The most frequently reported adverse reactions were related to the gastrointestinal tract. They were diarr dyspepsia and abdominal pain. Of 1,677 patients treated with Relafen in controlled clinical trials (1,140 followed for one year and 927 for two years), the cumulative incidence of peptic ulcers was 0.3% at 3 - 6 months, 0.5% at one year and 0.8% at two years.

The following table displays adverse events reported in long-term clinical trial follow-up involving treatment for up to 8 years. Adverse events listed at an estimated incidence of ≤ 0.01% are based on spontaneous reports from worldwide marketing experience. Where available, percentages are based upon the total number of observations, thus patients reporting multiple incidents of an adverse event have been recorded for each occurrence. Causal relationship to Relafen has not necessarily been established for all of the events listed below.

ADVERSE EVENTS:

Gastrointestinal: 14%-diarrhea, 13%-dyspepsia, 12%-abdominal pain, 9%-nausea, 6%-flatulence, 4%-constipation, 2%-positive stool guaiac, dry mouth, 1%-gastritis, vomiting, melena, 0.7%-eructation, gastroenteritis, 0.7%-anorexia, rectal bleeding, 0.4%-gastric ulcer, duodenal ulcer, stomatitis, 0.3%-dysphagia, 0.2%-increased appetite, glossitis, 0.1%-pancreatitis, gingivitis, duodenitis, bilirubinuria, gastrointestinal bleeding, ≤0.01%-cholestatic jaundice, gallstones.

Central Nervous System: 8%-headache, 6%-dizziness, 3%-insomnia, 2%-fatigue, somnolence, 1%-increased sweating, nervousness, 0.9%-depression, vertigo, 0.8%-malaise, paresthesia, 0.7%-asthenia, 0.4%-anxiety, 0.3%-confusion, 0.1%-agitation, tremor, <0.01%-nightmares.

Dermatologic: 7%-rash, 4%-pruritus, 0.9%-alopecia, 0.7%-urticaria, 0.4%-acne, 0.2%-bullous eruptions, photosensitivity, ≤0.01%-pseudoporphyria cutanea tarda, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis.

Special Senses: 4%-tinnitus, 2%-abnormal vision, 0.2%-taste disorder.

Cardiovascular: 1.7%-Hypertension, 1.0%-palpitations, 0.3%-syncope, 0.2%-thrombophlebitis, 0.1%-vasculitis, angina, arrhythmia, myocardial infarction.

Respiratory: 1%-dyspnea, 0.6%-cough, 0.4%-asthma, ≤0.01%-eosinophilic pneumonia, hypersensitivity pneumonitis.

Renal/Genitourinary: 0.7%-dysuria, 0.5%-albuminuria, 0.4%-hematuria, 0.2%-impotence, renal stones, 0.1%-hyperuricemia, azotemia, ≤0.01%-interstitial nephritis, vaginal bleeding.

Other: 0.7%-Edema, weight gain, 0.4%-weight loss, fever, 0.2%-chills, hyperglycemia, 0.1%-hypokalemia.

Hematologic/Lymphatic: 0.5%-anemia, 0.4%-leukopenia, 0.2%-thrombocytopenia, 0.1%-granulocytopenia, <0.01%-aplastic anemia.

Hepatic: 0.5%-Liver function abnormalities.

Allergic/Hypersensitivity: <0.01%-angioneurotic edema, anaphylactoid reaction, anaphylaxis.

SYMPTOMS AND TREATMENT OF OVERDOSAGE: Relafen (nabumetone) overdose has been rarely reported. If acute overdosage occurs, it is recommended that the stomach be emptied by vomiting or lavage and institution of general supportive measures as necessary. In addition, the use of activated charcoal, up to 60 g, may effectively reduce nabumetone absorption. Co-administration of nabumetone with activated charcoal orally in man has resulted in an 80% decrease in maximum plasma concentrations of the active metabolite.

DOSAGE AND ADMINISTRATION: *Osteoarthritis and Rheumatoid Arthritis:* The starting and usual adult dose is 1000 mg daily taken as a single dose with or without food. The dosage may be increased to 1500 mg or 2000 mg per day given either as a single dose or in two divided doses.

Since Relafen has an average plasma half-life of 23 hours in healthy young subjects and 30 hours in elderly patients, plasma levels of 6-MNA will approximate steady-state within one week of dosing. For this reason, dosage adjustments during therapy should not be made more frequently than at one week intervals, except in the case of side effects. In patients with severe renal or hepatic impairment, dosage level adjustments should be made on an individual basis.

AVAILABILITY OF DOSAGE FORMS: Relafen (nabumetone) is available as 500 mg tablets. These are white, pillow-shaped film coated tablets with RELAFEN embossed on one side and 500 embossed on the other side. The tablets are supplied in polyethylene bottles of 60 tablets per bottle.

PHARMACEUTICAL INFORMATION: *Composition:* In addition to the active ingredient, Relafen tablets contain the following non-medicinal ingredients: microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulphate, hydroxypropyl methylcellulose, and colouring and titanium dioxide in the film coating.

Stability and Storage. Relafen (nabumetone) should be stored between 15 - 30°C in a dry place and dispensed in a light-resistant container.

PHARMACOLOGY: Clinical: Double-blind studies of up to 6 months duration in rheumatoid arthritis and osteoarthritis have demonstrated that Relafen at a dosage of 1-2 g/day is at least as effective as daily doses of 3.6 g of acetylsalicylic acid (ASA), 1.6 g of ibuprofen, 75 - 150 mg of indomethacin, 100 mg of diclofenac and 500 mg - 1 g of naproxen. Long term follow-up studies of up to 8 years duration have shown that Relafen is well tolerated.

In five endoscopically-controlled studies comparing Relafen (102 patients treated at doses of 1 - 1.5 g/day) with naproxen (110 patients treated with doses of 500 mg - 1 g/day), Relafen caused significantly fewer gastric and duodenal ulcers than naproxen. In two studies of 1 g/day Relafen (n=78) compared with 600 mg ibuprofen q.i.d. alone (n=73) or in combination with 200 µg misoprostol (q.i.d.) (n=60), Relafen treatment resulted in significantly fewer gastric and duodenal ulcers than ibuprofen, and the frequency of ulcers with Relafen was not significantly different from the incidence of ulcers in patients taking misoprostol concomitantly with ibuprofen.

In two clinical pharmacology studies conducted in healthy volunteers, it was demonstrated that Relafen had little effect on collagen-induced platelet aggregation and no effect on bleeding time. Additionally, there was no evidence of serious hematological findings or clinically significant trends in hematological parameters associated with the use of Relafen in clinical trials.

Full Product Monograph available upon request.

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SmithKline Beecham Pharma

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For further information, please contact our medical department at 1-800-567-1550.

Pr cefzil*

cefprozil

Tablets, 250 and 500 mg
Powder for oral suspension, 125 mg/5mL and 250 mg/5mL
ANTIBIOTIC

ACTIONS AND CLINICAL PHARMACOLOGY

CEFZIL (cefprozil) is a semi synthetic broad spectrum cephalosporin antibiotic intended for oral administration. It has *in vitro* activity against a broad range of gram positive and gram negative bacteria. The bactericidal action of cefprozil results from inhibition of cell-wall synthesis.

Pharmacokinetics

Cefprozil is well absorbed following oral administration in both fasting and non-fasting subjects. The oral bioavailability of cefprozil is about 90%. The pharmacokinetics of cefprozil are not altered when administered with meals, or when co-administered with antacid. Average plasma concentrations after administration of cefprozil to fasting subjects are shown in the following table. Urinary recovery accounts for 60% of the administered dose.

Dosage	Mean Plasma Cefprozil* Concentrations (µg/mL)			8-hour Urinary Excretion
	Peak ~ 1.5 hr	4 hr	8 hr	
250 mg	6.1	1.7	0.2	60%
500 mg	10.5	3.2	0.4	62%
1 g	18.3	8.4	1.0	54%

*Data represent mean values from 12 healthy, young male volunteers.

During the first four-hour period after drug administration, the average urine concentrations following the 250 mg, 500 mg, and 1 g doses were approximately 170 µg/mL, 450 µg/mL and 600 µg/mL, respectively.

The average plasma half-life in normal subjects is 1.3 hours. Plasma protein binding is approximately 36% and is independent of concentration in the range of 2 µg/mL to 20 µg/mL. There is no evidence of accumulation of cefprozil in the plasma in individuals with normal renal function following multiple oral doses of up to 1 g every 8 hours for 10 days.

In patients with renal insufficiency

In patients with reduced renal function, the plasma half-life prolongation is related to the degree of the renal dysfunction and may be prolonged up to 5.2 hours. In patients with complete absence of renal function, the plasma half-life of cefprozil averaged 5.9 hours. The half-life is shortened during hemodialysis to 2.1 hours. Excretion pathways in patients with markedly impaired renal function have not been determined. (See PRECAUTIONS and DOSAGE AND ADMINISTRATION).

In patients with hepatic insufficiency

In patients with impaired hepatic function, no differences in pharmacokinetic parameters were observed, when compared to normal control subjects.

In elderly subjects

Following administration of a single 1 g dose of cefprozil, the average AUC observed in healthy elderly subjects (≥65 years of age) was approximately 35-60% higher than that of healthy young adults and the average AUC in females was approximately 15-20% higher than in males. The magnitude of these age and gender-related variations in the pharmacokinetics of cefprozil are not sufficient to necessitate dosage adjustments.

INDICATIONS AND CLINICAL USE

CEFZIL (cefprozil) is indicated for the treatment of the following infections caused by susceptible strains of the designated microorganisms:

UPPER RESPIRATORY TRACT

Pharyngitis / tonsillitis caused by *Streptococcus pyogenes.*

Substantial data establishing the efficacy of cefprozil in the subsequent prevention of rheumatic fever are not available at present, although no case was reported during its evaluation in over 978 pediatric and 831 adult patients in controlled clinical trials.

Otitis media caused by *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella (Branhamella) catarrhalis.*

SKIN AND SKIN STRUCTURE

Uncomplicated skin and skin-structure infections caused by *Staphylococcus aureus* (including penicillinase-producing strains) and *Streptococcus pyogenes.*

URINARY TRACT

Uncomplicated urinary tract infections (including acute cystitis) caused by *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis.*

Cultures and susceptibility studies should be performed when appropriate.

CONTRAINDICATIONS

CEFZIL (cefprozil) is contraindicated in patients with known allergy to the cephalosporin class of antibiotics or to any component of the cefprozil preparations.

WARNINGS

BEFORE THERAPY WITH CEFZIL (cefprozil) IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEFZIL, CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. IF THIS PRODUCT IS TO BE GIVEN TO PENICILLIN-SENSITIVE

PATIENTS, CAUTION SHOULD BE EXERCISED BECAUSE CROSS-SENSITIVITY AMONG BETA-LACTAM ANTIBIOTICS HAS BEEN CLEARLY DOCUMENTED AND MAY OCCUR IN UP TO 10% OF PATIENTS WITH A HISTORY OF PENICILLIN ALLERGY.

If an allergic reaction to CEFZIL occurs, discontinue the drug. Serious acute hypersensitivity reactions may require treatment with *epinephrine* and other emergency measures, including oxygen, intravenous fluids, intravenous antihistamines, corticosteroids, pressor amines, and airway management, as clinically indicated.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of "antibiotic-associated colitis". Pseudomembranous colitis is associated with the use of broad spectrum antibiotics (including macrolides, semisynthetic penicillins and cephalosporins) and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an oral antibacterial drug effective against *C. difficile* (e.g., metronidazole).

PRECAUTIONS

General

Evaluation of renal status before and during therapy is recommended, especially in seriously ill patients. In patients with known or suspected renal impairment (see DOSAGE AND ADMINISTRATION), careful clinical observation and appropriate laboratory studies should be done prior to and during therapy. The total daily dose of CEFZIL (cefprozil) should be reduced in patients with creatinine clearance values ≤30 mL/min because high and/or prolonged plasma antibiotic concentrations can occur from usual doses in such individuals. Cephalosporins, including CEFZIL, should be given with caution to patients receiving concurrent treatment with potent diuretics since these agents are suspected of adversely affecting renal function.

Prolonged use of CEFZIL may result in the overgrowth of non-susceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Positive direct Coombs tests have been reported during treatment with cephalosporin antibiotics.

Drug Interactions

Nephrotoxicity has been reported following concomitant administration of aminoglycoside antibiotics and cephalosporin antibiotics. Concomitant administration of probenecid doubled the area under the curve for cefprozil.

If an aminoglycoside is used concurrently with cefprozil, especially if high dosages of the former are used or if therapy is prolonged, renal function should be monitored because of the potential nephrotoxicity and ototoxicity of aminoglycoside antibiotics.

Drug/Laboratory Test Interactions

Cephalosporin antibiotics may produce a false positive reaction for glucose in the urine with copper reduction tests (Benedict's or Fehling's solution or with Clinitest tablets), but not with enzyme-based tests (glucose oxidase) for glycosuria. A false negative reaction may occur in the ferricyanide test for blood glucose. The presence of cefprozil in the blood does not interfere with the assay of plasma or urine creatinine by the alkaline picrate method.

Use in Pregnancy

Reproduction studies have been performed in mice, rats, and rabbits at doses 14, 7 and 0.7 times the maximum human daily dose (1000 mg) based upon mg/m², and have revealed no evidence of harm to the fetus due to cefprozil. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk.

Nursing Mothers

Less than 1.0% of a maternal dose is excreted in human milk. Caution should be exercised when CEFZIL is administered to a nursing mother. Consideration should be given to temporary discontinuation of nursing and use of formula feeding.

Pediatric Use

Safety and effectiveness in children below the age of 6 months have not been established. Accumulation of other cephalosporin antibiotics in newborn infants (resulting from prolonged drug half-life in this age group) has been reported.

Geriatric Use

Cefprozil has not been studied in the chronically ill or institutionalized elderly subjects. In these subjects, drug clearance by the kidney may be reduced even with normal serum creatinine clearance. Reduction of dose or of frequency of administration may be indicated.

ADVERSE REACTIONS

The adverse reactions to CEFZIL (cefprozil) are similar to those observed with other orally administered cephalosporins. Cefprozil was usually well tolerated in controlled clinical trials. Approximately 2% of patients discontinued cefprozil therapy due to adverse events.

The most common adverse events (of probable or unknown relationship to study drug) observed in 4227 patients treated with cefprozil in clinical efficacy trials are:

Gastrointestinal: Diarrhea (2.7%), nausea (2.3%), vomiting (1.4%) and abdominal pain (0.9%).

Hepatobiliary: As with some penicillins and some other cephalosporin antibiotics, cholestatic jaundice has been reported rarely.

Hypersensitivity: Rash (1.2%), erythema (0.1%), pruritus (0.3%) and urticaria (0.07%). Such reactions have been reported more frequently in children than in adults. Signs and symptoms usually occur a few days after initiation of therapy and subside within a few days after cessation of therapy.

CNS: Dizziness, hyperactivity, headache, nervousness, insomnia, confusion, and drowsiness have been reported rarely (< 1%) and causal relationship is uncertain. All were reversible.

Other: Genital pruritus (0.8%) and vaginitis (0.7%).

Laboratory abnormalities

Transitory abnormalities in clinical laboratory test results of uncertain etiology have been reported during clinical trials as follows:

Hepatobiliary: Elevations of AST, ALT, alkaline phosphatase, and bilirubin.

Hematopoietic: Transiently decreased leukocyte count and eosinophilia.

Renal: Slight elevations in BUN and serum creatinine.

Adverse reactions reported from post-marketing experience and which were not seen in the clinical trials include serum sickness, pseudomembranous colitis, Stephens Johnson syndrome and exfoliative dermatitis. The association between these events and CEFZIL administration is unknown.

In addition to the adverse reactions listed above which have been observed in patients treated with cefprozil, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics. Anaphylaxis, erythema multiforme, toxic epidermal necrolysis, fever, renal dysfunction, toxic nephropathy, aplastic anemia, hemolytic anemia, hemorrhage, prolonged prothrombin time, positive Coombs' tests, elevated LDH, pancytopenia, neutropenia, agranulocytosis, thrombocytopenia.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment, when the dosage was not reduced. (See DOSAGE AND ADMINISTRATION and OVERDOSAGE). If seizures associated with drug therapy occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Since no case of overdosage has been reported to date, no specific information on symptoms or treatment of overdosage is available. In animal toxicology studies, single doses as high as 5000 mg/kg were without serious or lethal consequences.

Cefprozil is eliminated primarily by the kidneys. In case of severe overdosage, especially in patients with compromised renal function, hemodialysis will aid in the removal of ceprozil from the body.

DOSAGE AND ADMINISTRATION

CEFZIL (cefprozil) is administered orally (with or without food), in the treatment of infections due to susceptible bacteria in the following doses:

Adults (13 years and older)

Upper respiratory tract (pharyngitis / tonsillitis):
500 mg q24h
Skin & skin structure:
250 mg q12h or 500 mg q24h
Uncomplicated urinary tract:
500 mg q24h

Children (2 years – 12 years)

Skin & skin structure: 20 mg/kg q24h

Weight (kg)	mg/day	Dose/ day	Multi-dose bottle			
			125 mg/5 mL		250 mg/5 mL	
			tsp/dose	mL/dose	tsp/dose	mL/dose
12.5	250	1	2.0	10.0	1.0	5.0
18.8	375	1	3.0	15.0	1.5	7.5
25	500	1	–	–	2.0	10.0
31.3	625	1	–	–	2.5	12.5
37.5	750	1	–	–	3.0	15.0

Infants and children (6 months-12 years)

Otitis media: 15 mg/kg q12h

Weight (kg)	mg/day	Doses/ day	Multi-dose bottle			
			125 mg/5 mL		250 mg/5 mL	
			tsp/dose	mL/dose	tsp/dose	mL/dose
8.3	250	2	1.0	5.0	0.5	2.5
12.5	375	2	1.5	7.5	0.75	3.75
16.7	500	2	2.0	10.0	1.0	5.0
20.8	625	2	2.5	12.5	1.25	6.25
25	750	2	3.0	15.0	1.5	7.5
29.2	875	2	-	-	1.75	8.75
≥ 33.3	1,000	2	-	-	2.0	10.0

Upper respiratory tract (pharyngitis / tonsillitis): 7.5 mg/kg q12h

Weight (kg)	mg/day	Doses/ day	Multi-dose bottle			
			125 mg/5 mL		250 mg/5 mL	
			tsp/dose	mL/dose	tsp/dose	mL/dose
8.3	125	2	0.5	2.5	–	–
16.7	250	2	1.0	5.0	0.5	2.5
25	375	2	1.5	7.5	0.75	3.75
33.3	500	2	2.0	10.0	1.0	5.0
41.7	625	2	2.5	12.5	1.25	6.25

The maximum pediatric daily dose should not exceed the maximum daily dose recommended for adults (i.e. 1 g per day).

Duration of Therapy

Duration of therapy in the majority of clinical trials was 10 to 15 days. The duration of treatment should be guided by the patient's clinical and bacteriological response. In the treatment of acute uncomplicated cystitis, a 7 day oral therapy is usually sufficient. In the treatment of infections due to *Streptococcus pyogenes*, a therapeutic dosage of CEFZIL should be administered for at least 10 days.

Renal Impairment

Cefprozil may be administered to patients with impaired renal function. No dosage adjustment is necessary for patients with creatinine clearance values > 30 mL/min. For those with creatinine clearance values ≤ 30 mL/min, 50% of the standard dose should be given at the standard dosing interval. Cefprozil is in part removed by hemodialysis; therefore, cefprozil should be administered after the completion of hemodialysis.

PHARMACEUTICAL INFORMATION

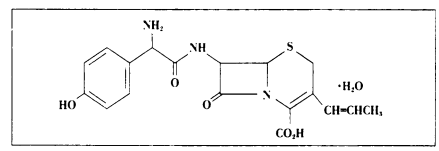
A. DRUG SUBSTANCE

Proper Name: Cefprozil

Chemical Name: (6R,7R)-7-[(R)-2-amino-2-(p-hydroxyphenyl) acetamido]-8-oxo-3-propenyl-5-thia-1-azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid

Empirical Formula: $C_{18}H_{19}N_3O_5S \cdot H_2O$

Structural Formula:



Molecular Weight: 407.45

Description: Cefprozil is a cis and trans isomeric mixture in a 9:1 ratio. It is a white to yellowish crystalline powder with a melting point of 197°C. It is poorly soluble (< 1mg/mL) in acetone, chloroform, ethanol and isopropanol and has an approximate solubility of 11 mg/mL in methanol and 1.6 mg/mL in demethyl sulfoxide. Cefprozil has an apparent octanol / water partition coefficient of 0.01 at pH6 and 22°C.

B. COMPOSITION

CEFZIL tablets contain cefprozil equivalent to 250 mg or 500 mg of anhydrous cefprozil. CEFZIL tablets also contain: microcrystalline cellulose, hydroxypropylmethylcellulose, magnesium stearate, simethicone, sodium starch glycolate, polyethylene glycol, polysorbate 80 and titanium dioxide. The 250 mg tablets also contain FD&C yellow No. 6.

CEFZIL powder for oral suspension contains cefprozil equivalent to 125 mg or 250 mg of anhydrous cefprozil per 5 mL of constituted solution.The powder for oral suspension also contains: aspartame, microcrystalline cellulose, citric acid, colloidal silicone dioxide, FD&C red No. 3, flavors (natural and artificial), glycine, polysorbate 80, simethicone, sodium benzoate, sodium carboxymethylcellulose, sodium chloride, and sucrose.

C. STORAGE

CEFZIL tablets and powder for oral suspension should be stored at room temperature (15 – 30°C) and protected from light and excessive humidity.

D. RECONSTITUTION

Prior to dispensing, the pharmacist must constitute the dry powder with water as follows:

CEFZIL powder for oral suspension	Bottle size (mL)	Diluent (water) added to bottle (mL)	Approximate available volume (mL)	Final concentration
125 mg/5 mL	75	54	75	125 mg/5 mL
	100	72	100	125 mg/5 mL
250 mg/5 mL	75	54	75	250 mg/5 mL
	100	72	100	250 mg/5 mL

For ease in preparation, the water can be added in two portions. Shake well after each addition and prior to use.

E. STORAGE OF RECONSTITUTED SUSPENSION

The constituted CEFZIL oral suspension can be stored in the refrigerator (2°C – 8°C) for up to 14 days. Keep container tightly closed. Discard unused portion after 14 days.

AVAILABILITY

CEFZIL (cefprozil) 250 mg tablets are light orange, caplet-shaped, film coated tablets embossed in red ink with 7720 and BMS 250.

CEFZIL (cefprozil) 500 mg tablets are white, caplet-shaped, film coated tablets embossed in red ink with 7721 and BMS 500.

CEFZIL 250 mg and 500 mg tablets are available in bottles of 100.

CEFZIL powder for oral suspension contains cefprozil, in a bubble-gum flavored mixture, equivalent to 125 mg or 250 mg cefprozil per 5 mL of constituted solution. Available in bottles of 75 and 100 mL.

Product Monograph available to physicians and pharmacists upon request.

1. Kessler RE, Fung-Tomc JC. *Infections in Medicine* 1992;9(Suppl C): 10-18 **2.** Cefzil Product Monograph, Bristol-Myers Squibb Canada Inc. **3.** Stutman HR. *Infections in Medicine* 1993;10(Suppl D):51-55. **4.** Thornsberry C et al. *Infections in Medicine* 1993;10(Suppl D): 15-24. **5.** Arguedas AG et al. *Pediatr Infect Dis J* 1991;10:375-380.

Bristol-Myers Squibb
Pharmaceutical Group

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PRANDASE®

PRESCRIBING INFORMATION

Acarbose

PrPRANDASE® (Acarbose) Tablets

THERAPEUTIC CLASSIFICATION
Oral Antidiabetic Agent
Alpha-glucosidase Inhibitor

ACTION AND CLINICAL PHARMACOLOGY: PRANDASE (acarbose) is a complex oligosaccharide that inhibits ∝-glucosidase activity in the brush border membrane of the small intestine. This delays the digestion of ingested carbohydrates, thereby resulting in a smoothing and lowering of blood glucose concentration following meals (postprandial). As a consequence of decreases in plasma glucose postprandial increases, PRANDASE reduces levels of glycosylated hemoglobin in patients with Type II (non-insulin dependent) diabetes mellitus. Systemic nonenzymatic protein glycosylation, as reflected by levels of glycosylated hemoglobin, is a function of average blood glucose concentration over time. **Mechanism of Action:** PRANDASE does not enhance insulin secretion. The antihyperglycemic action of acarbose results from a competitive, reversible inhibition of pancreatic ∝-amylase and membrane bound intestinal ∝-glucoside hydrolase enzymes. Pancreatic ∝-amylase hydrolyzes complex starches to oligosaccharides in the lumen of the smal intestine, while the membrane-bound intestinal ∝-glucosidases hydrolyze oligosaccharides, trisaccharides, and disaccharides to glucose and other monosaccharides in the brush border of the small intestine. In diabetic patients, this enzyme inhibition results in a delayed glucose absorption and a smoothing and lowering of postprandial hyperglycemia, resulting in improved glycemic control.Acarbose has no inhibitory activity against lactase and consequently does not induce lactose intolerance.

PHARMACOKINETICS: Absorption: One to 2% of an oral dose of acarbose is absorbed from the gastrointestinal tract as unchanged drug. When ^{14}C-labelled acarbose was administered orally, approximately 35% of the total radioactivity (changed and unchanged drug) was absorbed. An average of 51% of an oral dose was excreted in the feces as unabsorbed drug-related radioactivity within 96 hours of ingestion. Because acarbose acts locally within the gastrointestinal tract, this low systemic bioavailability of parent compound is therapeutically desired. Following oral dosing of healthy volunteers with ^{14}C-labelled acarbose, peak plasma concentrations of radioactivity were attained 14–24 hours after dosing, while peak plasma concentrations of active drug were attained at approximately 1 hour. The delayed absorption of acarbose-related radioactivity reflects the absorption of metabolites that may be formed by either intestinal bacteria or intestinal enzymatic hydrolysis. **Metabolism:** Acarbose is metabolized exclusively within the gastrointestinal tract, principally by intestinal bacteria, but also by digestive enzymes. A fraction of these metabolites (approximately 34% of the dose) was absorbed and subsequently excreted in the urine. At least 13 metabolites have been separated chromatographically from urine specimens. The major metabolites have been identified as 4-methylpyrogallol derivatives (i.e., sulfate, methyl, and glucuronide conjugates). One metabolite (formed by cleavage of a glucose molecule from acarbose) also has ∝-glucosidase inhibitory activity. This metabolite, together with the parent compound, recovered from the urine, accounts for less than 2% of the total administered dose. **Excretion:** The fraction of acarbose that is absorbed as intact drug is almost completely excreted by the kidneys. When acarbose was given intravenously, 89% of the dose was recovered in the urine as active drug within 48 hours. In contrast, less than 2% of an oral dose was recovered in the urine as active (i.e., parent compound and active metabolite) drug. This is consistent with the low bioavailability of the parent drug. The plasma elimination half-life of acarbose activity is approximately 2 hours in healthy volunteers. Consequently, drug accumulation does not occur with three times a day (t.i.d.) oral dosing. Patients with severe renal impairment (creatinine clearance < 25 mL/min/1.73m^2) attained about 5 times higher peak plasma concentrations of acarbose and 6 times larger AUCs than volunteers with normal renal function.

INDICATIONS AND CLINICAL USE: PRANDASE (acarbose) is indicated as adjunct to prescribed diet for the management of blood glucose levels in non-insulin dependent diabetic patients who are inadequately controlled by diet alone. In initiating treatment for NIDDM, diet should be emphasized as the primary form of treatment. Caloric restriction and weight loss are essential in the obese diabetic patient. Proper dietary management alone may be effective in controlling blood glucose and symptoms of hyperglycemia. The importance of regular physical activity when appropriate should also be stressed. If this treatment program fails to result in adequate glycemic control, the use of PRANDASE should be considered. The use of PRANDASE must be viewed by both the physician and patient as a treatment in addition to diet, and not as a substitute for diet or as a convenient mechanism for avoiding dietary restraint. PRANDASE should be considered as complementary to dietary therapy and physical exercise before resorting to other forms of treatment, such as oral hypoglycemics.

CONTRAINDICATIONS: PRANDASE (acarbose) is contraindicated in patients with hypersensitivity to acarbose and in patients with diabetic ketoacidosis. It is also contraindicated in patients with inflammatory bowel disease, colonic ulceration, partial intestinal obstruction or in patients predisposed to intestinal obstruction. In addition, PRANDASE should not be used in patients who have chronic intestinal diseases associated with marked disorders of digestion or absorption and in patients who suffer from states which may deteriorate as a result of increased gas formation in the intestine, eg. larger hernias.

WARNINGS: Transaminases: PRANDASE (acarbose), at doses usually in excess of 100 mg t.i.d., may give rise to elevations of serum transaminases and, in rare instances, hyperbilirubinemia. If elevated transaminase levels are observed, a reduction in dosage or withdrawal of therapy may be indicated, particularly if the elevations persist.

PRECAUTIONS: General: Increased use of sucrose (cane sugar) and food that contains sucrose can lead to gastrointestinal symptoms (eg. flatulence and bloating) and also loose stools and occasionally diarrhea as a result of increased carbohydrate fermentation in the colon during PRANDASE (acarbose) treatment. PRANDASE delays glucose absorption and lowers hyperglycemia following meals. Regular intake of PRANDASE should not be interrupted without the physician's knowledge, since such interruption can cause a rise in blood glucose. **Hypoglycemia:** Because of its mechanism of action, PRANDASE when administered alone will not cause hypoglycemia in the fasted or postprandial state. Sulfonylurea agents may cause hypoglycemia. Because PRANDASE given with a sulfonylurea will cause a further lowering of blood glucose, it may increase the hypoglycemic potential of the sulfonylurea. Oral glucose (dextrose), whose absorption is not inhibited by PRANDASE, should be used instead of sucrose (cane sugar) in the treatment of mild to moderate hypoglycemia. Sucrose, whose hydrolysis to glucose and fructose is inhibited by PRANDASE, is unsuitable for the rapid correction of hypoglycemia. Severe hypoglycemia may require the use of either intravenous glucose infusion or glucagon injection. **Loss of Control of Blood Glucose:** When diabetic patients are exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of control of blood glucose may occur. At such times, temporary insulin therapy may be necessary. **Use in the Elderly:** No special precautions are necessary with acarbose treatment in the elderly. Elderly patients receiving PRANDASE (acarbose) may require more intensive supervision and follow-up. **Use in Children:** Safety and effectiveness of PRANDASE in patients < 18 years of age have not been established. **Use in Obstetrics:** There are no adequate and well-controlled studies of PRANDASE in pregnant women and its use in these patients is not recommended. **Nursing Mothers:** A small amount of radioactivity has been found in the milk of lactating rats after administration of radiolabelled acarbose. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, PRANDASE should not be administered to a nursing woman. **Patients with Special Diseases and Conditions:** See "WARNINGS" regarding elevated serum transaminases. **Renal:** Plasma concentrations of PRANDASE in renally impaired volunteers were proportionally increased relative to the degree of renal dysfunction. Long-term clinical trials in diabetic patients with significant renal dysfunction (creatinine clearance <25 mL/min) have not been conducted. Therefore, treatment of these patients with PRANDASE is not recommended.In one species of rats studied an increased incidence of renal tumors was observed. This was not seen in any other species of rats or other animals studied. When malnutrition was prevented in these rats, acarbose did not increase the incidence of renal tumors.

DRUG INTERACTION: General: Certain drugs tend to produce hyperglycemia and may lead to loss of blood glucose control. These drugs include diuretics (thiazides, furosemide), corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics and isoniazid. When such drugs are administered to a patient receiving PRANDASE, the patient should be closely observed for loss of blood glucose control. **Intestinal Absorbents:** Intestinal absorbents (e.g., charcoal) and digestive enzyme preparations containing carbohydrate-splitting enzymes (amylase, pancreatin) may reduce the effect of PRANDASE and should not be taken concomitantly. **Antacids:** The concomitant administration of acarbose and an antacid does not alter the effect of acarbose. The administration of antacid preparations is unlikely to ameliorate the gastrointestinal symptoms of PRANDASE and therefore should not be recommended to patients for this purpose. **Cholestyramine:** The concomitant administration of cholestyramine may enhance the effects of PRANDASE, particularly with respect to reducing postprandial insulin levels. In healthy volunteers, a rebound phenomenon with respect to the postprandial insulin response was observed when both acarbose and cholestyramine therapy were withdrawn simultaneously. **Other Drugs:** Studies in healthy volunteers have shown that PRANDASE has no effect on either the pharmacokinetics or pharmacodynamics of digoxin, nifedipine, propranolol or ranitidine. PRANDASE did not interfere with the absorption or disposition of the sulfonylurea glyburide in diabetic patients. PRANDASE delays the intestinal absorption of metformin but does not reduce its overall bioavailability. **Laboratory Tests:** Therapeutic response to PRANDASE should be monitored by periodic postprandial blood glucose tests. Measurement of glycosylated hemoglobin levels is recommended for the monitoring of long-term glycemic control.

ADVERSE REACTIONS: In placebo controlled pivotal studies of ≥6 months duration, adverse experiences were reported in 50% of patients receiving placebo and in 75% of patients treated with PRANDASE (acarbose). The majority of adverse experiences were gastrointestinal symptoms which result from the pharmacodynamic action of the drug. The majority of symptoms were of mild or moderate intensity and were dose-dependent. The symptoms occurred early (within 1–2 months of treatment) and improved tolerability with longer duration of treatment was observed. Rarely, these gastrointestinal events may be severe and might be confused with ileus/ileus-like symptoms. Therapy was discontinued prematurely due to adverse events in 13% of acarbose-treated patients and 4% of placebo-treated patients. The following adverse events (> 3%) were reported:

	Incidence of Adverse Events (%) Diet	
Adverse Event	**Acarbose**	**Placebo**
	n = 192	n = 196
Flatulence	127 (66)	58 (30)
Diarrhea	49 (26)	17 (8.7)
Abdominal Pain	22 (11)	11 (5.7)
Abdominal Cramps	10 (5.2)	5 (2.6)
Abdominal Distension	6 (3.1)	3 (1.5)
Nausea	7 (3.6)	5 (2.6)
Dyspepsia	9 (4.7)	9 (4.6)
Constipation	15 (7.7)	5 (2.6)
Flu Syndrome	12(6.3)	14 (7.1)
Headache	10(5.2)	5 (2.6)

The only significant difference in the incidence of adverse events between PRANDASE and placebo were gastrointestinal symptoms (eg. flatulence, diarrhea and abdominal pain) which can be minimized by starting on a low dose and titrating slowly (see DOSAGE AND ADMINISTRATION).Rarely, hypersensitive skin reactions, such as erythema, exanthema and urticaria, may occur. **Laboratory Tests:** In clinical trials, at doses of 50 mg t.i.d. and 100 mg t.i.d., the incidence of serum transaminase elevations with PRANDASE was the same as with placebo. In international postmarketing experience with PRANDASE in over 500,000 patients, rare instances of serum transaminase elevations ≥ 500 IU/L have been reported, some of which were associated with jaundice. In most of these instances, the dosage of acarbose was 100 mg t.i.d. or greater. In cases where follow-up was reported, hepatic dysfunction improved or resolved upon discontinuation of PRANDASE.

SYMPTOMS AND TREATMENT OF OVERDOSE: An overdose of PRANDASE (acarbose) will not result in hypoglycemia. When PRANDASE is taken with drinks and/or meals containing carbohydrates (polysaccharides, oligosaccharides, or disaccharides), overdosage can lead to abdominal distension, flatulence, and diarrhea. In the event of PRANDASE being taken in an overdose independent of food, excessive intestinal symptoms need not be anticipated.In cases of overdosage, the patient should not be given drinks or meals containing carbohydrates (polysaccharides, oligosaccharides, and disaccharides) for the next 4–6 hours.

DOSAGE AND ADMINISTRATION: There is no fixed dosage regimen for the management of diabetes mellitus with PRANDASE (acarbose) or any other pharmacologic agent. Dosage of PRANDASE must be individualized on the basis of both effectiveness and tolerance while not exceeding 100 mg t.i.d. PRANDASE should be taken three times daily with the first bite of each main meal. PRANDASE should be started at a low dose, with gradual dose escalation as described below; both to reduce gastrointestinal side effects and to permit identification of the minimum dose required for adequate glycemic control of the patient. During treatment initiation and dose titration (see below), two-hour postprandial plasma glucose should be used to determine the therapeutic response to PRANDASE and identify the minimum effective dose for the patient. Thereafter, glycosylated hemoglobin should be measured at intervals of approximately three months. The therapeutic goal should be to decrease both postprandial plasma glucose and glycosylated hemoglobin levels to optimal or near optimal by using the lowest effective dose of PRANDASE (see Canadian Diabetes Association Board Guidelines).**Initial Dosage:** The usual starting dosage of PRANDASE is 25 mg (half of a 50 mg tablet), given orally three times daily with the first bite of each main meal.**Maintenance Dosage:** Dosage of PRANDASE should be adjusted at 4–8 week intervals based on two-hour postprandial glucose levels and on tolerance. After the initial dosage of 25 mg t.i.d., the dosage should be increased to 50 mg t.i.d. Some patients may benefit from further increasing the dosage to 100 mg t.i.d. The maintenance dose ranges from 50 mg t.i.d. to 100 mg t.i.d. Consideration should be given to lowering the dose if no further reduction in postprandial glucose or glycosylated hemoglobin levels is observed after titration to 100 mg t.i.d. Once an effective and tolerated dosage is established, it should be maintained. **Maximum Dosage:** Dosages above 100 mg t.i.d. are not recommended.

PHARMACEUTICAL INFORMATION: i) Drug Substance: Acarbose is a oligosaccharide. It contains acarviosine, an unsaturated cyclitol unit linked to an amino sugar, bonded to a maltose unit. Common Name: Acarbose. Structural Formula: Chemical Name: O-4,6-dideoxy-4-[[(1S, 4R, 5S, 6S)-4,5,6-trihydroxy-3-(hydroxymethyl)-2-cyclohexen-1- yl]amino]- ∝ -D-glucopyranosyl-(1→4)-O- ∝ -D-glucopyranosyl-(1→4)-D-glucose.Molecular Formula: $C_{25}H_{43}NO_{18}$ Molecular Weight: 645.6 Description: Acarbose is a white to off-white powder. It remains stable for several hours in dilute acid (0.1M HCl), alkali (0.1M NaOH), at pH 7 and at body temperature (37-40°C). Acarbose is soluble in water and has a pKa of 5.1. Solubility: In water, approximately 140 g/100 mL at 20°C. ii)Composition of Dosage Forms: PRANDASE tablets contain 50 or 100 mg of acarbose.Non-medicinal ingredients: corn starch, microcrystalline cellulose, silicon dioxide, magnesium stearate. The formulation contains no preservatives or colouring agents. iii) Stability and Storage Recommendations: Storage should be below 25°C. At temperatures >25°C and at a relative humidity of >75%, discolouration may occur in tablets that have been removed from the pack. The tablets should therefore not be removed from the foil until immediately before use.

AVAILABILITY: PRANDASE (acarbose) 50 and 100 mg tablets are available in blister packs in cartons of 120 tablets. Tablets are round and off-white in colour. The 50 mg tablet is marked with "G50" on one side and the Bayer cross on the other; the 100 mg tablet is marked with "G100" on one side and the Bayer cross on the other.

References
1. Hanefeld, Pract Diab Supp. 1993: Vol. 10 No. 6. 2. Chiasson et al, Ann Intern Med. 1994; 121: 928 - 935. 3. Hanefeld et al, Diabetes Care, 1991; Vol. 14 : No 8: 732 - 737. 4. Product Monograph

Product monograph available upon request

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PAAB

PR110-0196E

PROZAC®

fluoxetine hydrochloride

AS YOUR FIRST LINE OF ACTION

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PROZAC® (fluoxetine hydrochloride) CAPSULES AND ORAL SOLUTION

THERAPEUTIC CLASSIFICATION Antidepressant/Antiobsessional/Antibulimic Agent

INDICATIONS *Depression:* PROZAC (fluoxetine) is indicated for the symptomatic relief of depressive illness. *Bulimia Nervosa:* PROZAC has been shown to significantly decrease binge-eating and purging activity when compared with placebo treatment. *Obsessive-Compulsive Disorder:* PROZAC has been shown to significantly reduce the symptoms of obsessive-compulsive disorder in double-blind, placebo-controlled clinical trials. The obsessions or compulsions must be experienced as intrusive, markedly distressing, time consuming, or interfering significantly with the person's social or occupational functioning. The efficacy of PROZAC in hospitalized patients has not been adequately studied. The effectiveness of PROZAC in long-term use (i.e. for more than 5 to 6 weeks in depression, for more than 16 weeks in bulimia nervosa, or for more than 13 weeks in obsessive compulsive disorder), has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use PROZAC for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS PROZAC (fluoxetine) is contraindicated in patients with known hypersensitivity to the drug. Monoamine Oxidase Inhibitors – There have been reports of serious, sometimes fatal, reactions (including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma) in patients receiving PROZAC in combination with a monoamine oxidase inhibitor (MAOI), and in patients who have recently discontinued PROZAC and then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Therefore, **PROZAC should not be used in combination with an MAOI, or within 14 days of discontinuing therapy with an MAOI.** Since fluoxetine and its major metabolite have very long elimination half-lives, at least 5 weeks should be allowed after stopping PROZAC before starting an MAOI. Limited reports suggest that intravenously administered dantrolene (Dantrium®) or orally administered cyproheptadine (Periactin®) may benefit patients experiencing such reactions.

WARNINGS *Allergic Reactions* (Rash and Accompanying Events): During premarketing testing of more than 5,600 patients given PROZAC (fluoxetine) approximately 4% developed a rash and/or urticaria. Among these cases, almost a third were withdrawn from treatment because of the rash and/or systemic signs or symptoms associated with the rash. Clinical findings reported in association with these allergic reactions include rash, fever, leukocytosis, arthralgias, edema, carpal tunnel syndrome, respiratory distress, lymphadenopathy, proteinuria, and mild transaminase elevation. Most patients improved promptly with discontinuation of fluoxetine and/or adjunctive treatment with antihistamines or steroids, and all patients experiencing these events were reported to recover completely. In premarketing clinical trials two patients are known to have developed a serious cutaneous systemic illness. In neither patient was there an unequivocal diagnosis, but one was considered to have a leukocytoclastic vasculitis, and the other severe desquamation that was considered variously to be a vasculitis or erythema multiforme. Other patients have had systemic manifestations suggestive of serum sickness. Since the introduction of fluoxetine, systemic events, possibly related to vasculitis, have developed in patients with rash. Although these events are rare, they may be serious, involving the lung, kidney, or liver. Death has been reported to occur in association with these systemic events. Anaphylactoid events, including bronchospasm, angioedema, and urticaria alone and in combination, have been reported. Pulmonary events, including inflammatory processes of varying histopathology and/or fibrosis, have been reported rarely. These events have occurred with dyspnea as the only preceding symptom. Whether these systemic events and rash have a common underlying cause or are due to different etiologies or pathogenic processes is not known. Furthermore, a specific underlying immunologic basis for these events has not been identified. Upon the appearance of rash or of other possibly allergic phenomena for which an alternative etiology cannot be identified, PROZAC should be discontinued. Particular caution should be exercised in patients with a history of allergic reactions. *Implications of the Long Elimination Half-Life of Fluoxetine:* Because of the long elimination half-lives of fluoxetine and its major active metabolite norfluoxetine, changes in dose will not be fully reflected in plasma for several weeks, affecting both strategies for titration to final dose and withdrawal from treatment (see ACTIONS and DOSAGE AND ADMINISTRATION). Even when dosing is stopped, active drug substance will persist in the body for weeks due to the long elimination half-lives of fluoxetine and norfluoxetine. This is of potential consequence when drug discontinuation is required or when drugs are prescribed that might interact with fluoxetine and norfluoxetine following discontinuation of PROZAC.

PRECAUTIONS *Anxiety and Insomnia:* During premarketing clinical trials anxiety, nervousness and insomnia were reported by 10 to 15% of patients treated with PROZAC (fluoxetine). These symptoms led to discontinuation of the drug in 5% of the patients. *Weight Change:* Significant weight loss, especially in underweight depressed patients and the elderly, may be an undesirable result of treatment with PROZAC. *Mania/Hypomania:* During premarketing clinical trials in a patient population comprised primarily of unipolar depressives, hypomania or mania occurred in approximately 1% of fluoxetine treated patients. The incidence in a general patient population which might also include bipolar depressives is unknown. The likelihood of hypomanic or manic episodes may be increased at the higher dosage levels. Such reactions require a reduction in dosage or discontinuation of the drug. *Seizures:* PROZAC should be used with caution in patients with a history of convulsive disorders. The incidence of seizures associated with fluoxetine during clinical trials did not appear to differ from that reported with other marketed antidepressants; however, patients with a history of convulsive disorders were excluded from these trials. Concurrent administration with electroshock therapy should be avoided because of the absence of experience in this area. There have been rare reports of prolonged seizures in patients on fluoxetine receiving ECT treatment. *Hypokalemia:* Self-induced vomiting often leads to hypokalemia which may lower seizure threshold and/or may lead to cardiac conduction abnormalities. Electrolyte levels of bulimic patients should be assessed prior to initiation of treatment. *Suicide:* The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Therefore, high risk patients should be closely supervised throughout therapy and consideration should be given to the possible need for hospitalization. In order to minimize the opportunity for overdosage, prescriptions for fluoxetine should be written for the smallest quantity of drug consistent with good patient management. *Concomitant Illness:* Clinical experience with PROZAC in patients with concomitant systemic illness is limited and it should be used cautiously in such patients, especially those with diseases or conditions that could affect metabolism or hemodynamic responses. PROZAC has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were systematically excluded from premarketing clinical studies. Retrospective evaluation of EKGs in some of these studies showed no conduction abnormalities that resulted in heart block. The mean heart rate was reduced by approximately 3 beats/minute. PROZAC should be given with caution to patients suffering from anorexia nervosa and only if the expected benefits (e.g. co-morbid depression) markedly outweigh the potential weight reducing effect of the drug. In patients with diabetes, fluoxetine may alter glycemic control. Hypoglycemia has occurred during therapy with fluoxetine, and hyperglycemia has developed following discontinuation of the drug. As is true with many other types of medication when taken concurrently by patients with diabetes, insulin and/or oral hypoglycemic dosage may need to be adjusted when therapy with fluoxetine is instituted or discontinued. Since fluoxetine is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. However, until an adequate number of patients with severe renal impairment have been evaluated in the course of chronic treatment, fluoxetine should be used with caution in such patients. Since clearances of fluoxetine and norfluoxetine may be decreased in patients with impaired liver function including cirrhosis, a lower or less frequent dose should be used in such patients. *Hyponatremia:* Several cases of hyponatremia (some with serum sodium lower than 110 mmol/L) have been reported. The hyponatremia appeared to be reversible when PROZAC was discontinued. Although these cases were complex with varying possible etiologies, some were possibly due to the syndrome of inappropriate antidiuretic hormone secretion (SIADH). The majority of these occurrences have been in older patients and in patients taking diuretics or who were otherwise volume depleted. In a placebo-controlled, double-blind trial in elderly patients, 10 of 313 fluoxetine treated patients and 6 of 320 placebo-treated patients had a lowering of serum sodium below the reference range. The lowest observed concentration of sodium in a fluoxetine treated patient was 129 mmol/L. *Platelet Function:* There have been rare reports of altered platelet function and/or abnormal results from laboratory studies in patients taking fluoxetine. While there have been reports of abnormal bleeding in several patients taking fluoxetine, it is unclear whether fluoxetine had a causative role. *Cognitive and Motor Performance:* Patients should be cautioned against driving an automobile or performing hazardous tasks until they are reasonably certain that treatment with PROZAC does not affect them adversely. *Use in Pregnancy and Lactation:* Safe use of fluoxetine during pregnancy and lactation has not been established. Therefore PROZAC should not be administered to women of childbearing potential or nursing mothers unless, in the opinion of the treating physician, the expected benefits to the patient markedly outweigh the possible hazards to the fetus or the child. In one breast milk sample, the concentration of fluoxetine plus norfluoxetine was 70.4 ng/mL. The concentration in the mother's plasma was 295.0 ng/mL. No adverse effects on the infant were reported. In another case, a 6-week infant, nursed by a mother on PROZAC, developed crying, decreased sleep, vomiting and watery stools. The breast milk showed concentrations of 69 ng/mL for fluoxetine and 90 ng/mL for norfluoxetine. In the infant's plasma, the concentrations of fluoxetine and norfluoxetine were 340 and 208 ng/mL, respectively. *Use in Children:* Safety and effectiveness in patients below the age of 18 have not been established. *Use in the Elderly:* Evaluation of patients over the age of 60 who received PROZAC 20 mg daily revealed no unusual pattern of adverse events relative to the clinical experience in younger patients. These data are however insufficient to rule out possible age-related differences during chronic use, particularly in elderly patients who have concomitant systemic illnesses or who are receiving concomitant drugs. *Drug Interactions:* Combined use of PROZAC and MAO inhibitors is contraindicated (see CONTRAINDICATIONS). There have been greater than 2-fold increases of previously stable plasma levels of other antidepressants when PROZAC has been administered in combination with these agents. There have been reports of both increased and decreased lithium levels when lithium was used concomitantly with fluoxetine. Cases of lithium toxicity have been reported. Lithium levels should be monitored when these drugs are administered concomitantly. Five patients receiving PROZAC in combination with tryptophan experienced adverse reactions, including agitation, restlessness and gastrointestinal distress. The half-life of concurrently administered diazepam may be prolonged in some patients. Experience with the use of PROZAC in combination with other CNS-active drugs is limited and caution is advised if such concomitant medication is required (see WARNINGS). *Phenytoin:* In patients on stable, maintenance doses of phenytoin, plasma phenytoin concentrations increased substantially and symptoms of phenytoin toxicity appeared (nystagmus, diplopia, ataxia and CNS depression) following initiation of concomitant fluoxetine treatment. *Drugs Tightly Bound to Plasma Protein:* Because fluoxetine is highly bound to plasma protein, the administration of fluoxetine to a patient taking another drug which is tightly bound to protein (e.g. warfarin, digitoxin) may cause a shift in plasma concentrations potentially resulting in an adverse effect. Conversely, adverse effects may result from displacement of protein bound fluoxetine by other tightly bound drugs. *P450 isozyme (IID6):* Like other selective serotonin reuptake inhibitors, Prozac inhibits the specific hepatic cytochrome P450 isozyme (IID6) which is responsible for the metabolism of debrisoquine and sparteine. Although the clinical significance of this effect has not been established, inhibition of IID6 may lead to elevated plasma levels of co-administered drugs which are metabolized by this isozyme. Drugs metabolized by cytochrome P450IID6 include the tricyclic antidepressants (e.g. nortriptyline, amitriptyline, imipramine, and desipramine), phenothiazine neuroleptics (e.g. perphenazine and thioridazine), and Type IC antiarrhythmics (e.g. propafenone and flecainide). *Dependence Liability:* PROZAC has not been systematically studied, in animals or humans, for its potential for abuse, tolerance, or physical dependence. Physicians should carefully evaluate patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of PROZAC.

ADVERSE REACTIONS *Commonly Observed:* In clinical trials, the most commonly observed adverse events associated with the use of PROZAC (fluoxetine) and not seen at an equivalent incidence among placebo treated patients were: central nervous system complaints, including headache, nervousness, insomnia, drowsiness, fatigue or asthenia, anxiety, tremor, and dizziness or lightheadedness; gastrointestinal complaints, including nausea, diarrhea, dry mouth and anorexia; and excessive sweating. *Adverse Events Leading to Discontinuation of Treatment:* Fifteen percent of approximately 4,000 patients who received PROZAC in North American clinical trials discontinued treatment due to an adverse event. The more common events causing discontinuation from depression trials in adults and elderly, included: psychiatric, primarily nervousness, anxiety, and insomnia; digestive, primarily nausea; nervous system, primarily dizziness, asthenia, and headaches; skin, primarily rash and pruritus. In obsessive compulsive disorder studies, 12.1% of fluoxetine treated patients discontinued treatment early because of adverse events. Anxiety, and rash, at incidences of less than 2%, were the most frequently reported events. In bulimia nervosa studies, 10.2% of fluoxetine treated patients discontinued treatment early because of adverse events. Insomnia, anxiety and rash, at incidences of less than 2%, were the most frequently reported events. *Serious Adverse Reactions:* Suicidal thoughts and acts are far more common among depressed patients than in the general population. It is estimated that suicide is 22 to 36 times more prevalent in depressed persons than in the general population. A comprehensive meta-analysis of pooled data from 17 double-blind clinical trials in patients with major depressive disorder compared fluoxetine (n=1765) with a tricyclic antidepressant (n=731) or placebo (n=569), or both. The pooled incidence of emergence of substantial suicidal ideation was 1.2% for fluoxetine, 2.6% for placebo, and 3.6% for tricyclic antidepressants. In countries where the drug has already been marketed, the following potentially serious adverse reactions have been reported; interactions with MAO inhibitors and possibly other drugs, allergic reactions, cardiovascular reactions, syndrome of inappropriate ADH secretion, and grand mal seizure. Death and life-threatening events have been associated with some of these reactions, although causal relationship to PROZAC has not necessarily been established. Postmarketing experience also confirms the profile of adverse reactions commonly reported during clinical trials with PROZAC including allergic skin reactions. *Adverse Experience Reports:* The pattern of treatment-emergent adverse experience incidence (≥5%) for both fluoxetine and placebo was somewhat different in bulimia and obsessive compulsive disorder trials than in the adult and elderly depression studies, and is summarized below:

	Percentage of Patients Reporting Event							
	DEPRESSION (Adults)		**DEPRESSION (Elderly)**		**OCD**		**BULIMIA**	
Body System/ Adverse Event	Fluoxetine (N=1730)	Placebo (N=799)	Fluoxetine (N=335)	Placebo (N=336)	Fluoxetine (N=264)	Placebo (N=89)	Fluoxetine (N=418)	Placebo (N=210)
Nervous								
Headache	20.3	15.5	27.5	23.8	32.6	23.6	30.1	26.9
Nervousness	14.9	8.5	12.2	7.4	14.4	14.6	10.8	5.2
Insomnia	13.8	7.1	18.2	12.5	29.6	22.5	33.1	15.0
Somnolence	11.6	6.3	9.3	5.7	17.1	6.7	12.7	7.1
Anxiety	9.4	5.5	13.1	8.0	13.6	6.7	16.3	11.1
Tremor	7.9	2.4	7.8	3.9	9.1	1.1	13.7	2.0
Dizziness	5.7	3.3	11.0	10.1	13.3	11.2	11.4	5.4
Libido, decreased	1.6	–	–	–	11.4	2.3	5.9	0.9
Depression	–	–	–	–	8.0	14.6	10.1	16.4
Emotional labiility	–	–	–	–	–	–	2.7	7.8
Digestive								
Nausea	21.1	10.1	16.7	7.4	26.5	13.5	29.7	13.5
Diarrhea	12.3	7.0	14.3	8.9	18.2	13.5	7.5	6.7
Dry mouth	9.5	6.0	6.6	4.8	12.1	3.4	9.9	8.6
Anorexia	8.7	1.5	10.7	1.8	16.7	10.1	8.8	4.4
Dyspepsia	6.4	4.3	11.0	5.1	9.9	4.5	10.7	6.7
Gastrointestinal disorder	–	–	–	–	5.7	1.1	5.7	5.9
Constipation	–	–	6.9	6.3	4.2	6.7	4.8	4.6
Flatulence	–	–	7.2	2.4	3.4	5.6	–	–
Skin and Appendages								
Sweating, excessive	8.4	3.8	7.2	3.3	7.2	–	8.9	1.6
Rash	–	–	–	–	6.4	3.4	5.1	4.9
Body as a Whole								
Asthenia	4.4	1.9	12.8	10.1	15.2	10.1	21.7	9.6
Flu syndrome	–	–	–	–	9.9	6.7	10.1	5.9
Back Pain	–	–	6.9	8.6	2.7	5.6	3.9	7.0
Infection	–	–	–	–	–	–	6.2	6.2
Abdominal Pain	–	–	6.0	5.7	4.9	11.2	9.6	6.5
Myalgia	–	–	3.3	5.4	–	–	4.7	9.4
Respiratory								
Upper respiratory infection	7.6	6.0	–	–	–	–	–	–
Rhinitis	–	–	9.0	14.3	22.7	23.6	23.0	29.1
Pharyngitis	–	–	–	–	10.6	9.0	11.1	5.5
Sinusitis	–	–	3.3	6.8	–	–	5.7	6.9
Yawn	–	–	–	–	7.2	–	11.1	0.8
Cardiovascular								
Vasodilatation	–	–	–	–	5.3	–	–	–
Urogenital								
Menstrual disorder	–	–	–	–	3.4	5.6	8.3	4.8
Dysmenorrhea	–	–	–	–	3.4	5.6	6.1	7.8
Urinary frequency	–	–	–	–	–	–	6.2	1.6
Urinary tract infection	–	–	–	–	–	–	5.1	2.0

DOSAGE AND ADMINISTRATION Since it may take up to four or five weeks to reach steady-state plasma levels of PROZAC (fluoxetine), sufficient time should be allowed to elapse before dosage is gradually increased. Higher dosages are usually associated with an increased incidence of adverse reactions. **Depression:** *Initial Adult Dosage:* The usual initial dosage is 20 mg administered once daily in the morning. A gradual dose increase should be considered only after a trial period of several weeks if the expected clinical improvement does not occur. Dosage should not exceed a maximum of 80 mg per day since clinical experience with doses above 80 mg per day is very limited. *Use in the Elderly:* Fluoxetine was in depressed elderly patients evaluated only at a dosage of 20 mg/day. A lower or less frequent dosage may be effective and should be considered in elderly patients with concurrent disease or on multiple medications. *Use in Children:* The safety and effectiveness of PROZAC in patients below the age of 18 years have not been established. **Bulimia Nervosa:** *Adult Dosage:* The recommended dosage is 60 mg per day, although studies show that lower doses may also be efficacious. Electrolyte levels should be assessed prior to initiation of treatment. **Obsessive-Compulsive Disorder:** A dose range of 20 mg/day to 60 mg/day is recommended for the treatment of obsessive-compulsive disorder. For any indication, the total fluoxetine dosage should not exceed a maximum of 80 mg per day since clinical experience with doses above 80 mg per day is very limited. During maintenance therapy, the dosage should be kept at the lowest effective level. **A lower or less frequent dosage should be used in patients with renal and/or hepatic impairment and in those on multiple medications.**

AVAILABILITY PROZAC (fluoxetine hydrochloride) 10 mg capsules are green and grey, printed with Lilly 3104 and Prozac 10 mg, packaged in amber HDPE bottles of 30 and 100. DIN 02018985

PROZAC (fluoxetine hydrochloride) 20 mg capsules are green and white, printed with Lilly 3105 and Prozac 20 mg, packaged in amber HDPE bottles of 100. DIN 00636622

PROZAC (fluoxetine hydrochloride) liquid is a clear colourless syrup solution 20 mg/5 mL, an odour of mint, packaged in amber glass bottles of 120 mL (M-5120). DIN 01917021

Storage: Store at 15° – 25° C.

PROZAC is a schedule F drug and cannot be obtained without a written order from a licensed practitioner.

PRODUCT MONOGRAPH AVAILABLE ON REQUEST. SEPTEMBER 1994

Lilly Eli Lilly Canada Inc. Scarborough, Ontario PAAB CCPP MEMBER PMAC

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ALTACE®
ramipril

PHARMACOLOGIC CLASSIFICATION: Angiotensin Converting Enzyme Inhibitor

INDICATIONS AND CLINICAL USE: Treatment of essential hypertension. It may be used alone or in association with thiazide diuretics.

In using ALTACE consideration should be given to the risk of angioedema (see WARNINGS).

ALTACE should normally be used in patients in whom treatment with a diuretic or a beta blocker was found ineffective or has been associated with unacceptable adverse effects.

ALTACE can also be tried as an initial agent in those patients in whom use of diuretics and/or beta blockers are contraindicated or in patients with medical conditions in which these drugs frequently cause serious adverse effects.

The safety and efficacy of ALTACE in congestive heart failure and renovascular hypertension have not been established and therefore, its use in these conditions is not recommended.

The safety and efficacy of concurrent use of ALTACE with antihypertensive agents other than thiazide diuretics have not been established.

When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury or even death of the developing fetus. When pregnancy is detected ALTACE should be discontinued as soon as possible (see WARNINGS – Use in Pregnancy).

CONTRAINDICATIONS: ALTACE (ramipril) is contraindicated in patients who are hypersensitive to this drug, or to any ingredient in the formulation, or in those patients who have a history of angioedema.

WARNINGS: Angioedema: Angioedema has been reported in patients with ACE inhibitors, including ALTACE (ramipril). Angioedema associated with laryngeal involvement may be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, ALTACE should be discontinued immediately, the patient treated appropriately in accordance with accepted medical care, and carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment, although antihistamines may be useful in relieving symptoms. Where there is involvement of tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy (including, but not limited to 0.3 to 0.5 mL of subcutaneous epinephrine solution 1:1000) should be administered promptly (see ADVERSE REACTIONS).

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see CONTRAINDICATIONS).

Hypotension: Symptomatic hypotension has occurred after administration of ALTACE, usually after the first or second dose or when the dose was increased. It is more likely to occur in patients who are volume depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. In patients with ischemic heart disease or cerebrovascular disease, an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident (see ADVERSE REACTIONS). Because of the potential fall in blood pressure in these patients, therapy with ALTACE should be started under close medical supervision. Such patients should be followed closely for the first weeks of treatment and whenever the dose of ALTACE is increased. In patients with severe congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension and has been associated with oliguria, and/or progressive azotemia, and rarely, with acute renal failure and/or death.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of 0.9% sodium chloride. A transient hypotensive response is not a contraindication to further doses which usually can be given without difficulty once the blood pressure has increased after volume expansion. However, lower doses of ALTACE and/or reduced concomitant diuretic therapy should be considered.

Neutropenia/Agranulocytosis: Agranulocytosis and bone marrow depression have been caused by ACE inhibitors. Several cases of agranulocytosis, neutropenia or leukopenia have been reported in which a causal relationship to ALTACE cannot be excluded. Current experience with the drug shows the incidence to be rare. Periodic monitoring of white blood cell counts should be considered, especially in patients with collagen vascular disease and/or renal disease.

Use in Pregnancy: ACE inhibitors can cause fetal and neonatal morbidity and mortality when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ALTACE should be discontinued as soon as possible.

PRECAUTIONS: Renal Impairment: Renal function should be assessed before initiating therapy with ALTACE (ramipril).

ALTACE should be used with caution in patients with renal insufficiency as they may require reduced or less frequent doses (see DOSAGE AND ADMINISTRATION). Close monitoring of renal function during therapy should be performed as deemed appropriate in those with renal insufficiency. In the majority, renal function will not alter, or may improve.

In patients with severe heart failure, whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including ALTACE, may be associated with oliguria and/or progressive azotemia and rarely acute renal failure and/or death.

In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine have been observed in some patients following ACE inhibitor therapy. These increases were almost always reversible upon discontinuation of the ACE inhibitor and/or diuretic therapy. In such patients renal function should be closely monitored.

Some hypertensive patients, with no apparent pre-existing renal disease have developed increases in blood urea nitrogen and creatinine especially when ALTACE has been given concurrently with a diuretic. Dosage reduction and/or discontinuation of the diuretic and/or ALTACE may be required.

Anaphylactoid Reactions during Membrane Exposure: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes (e.g. polyacrylonitrile [PAN]) and treated concomitantly with an ACE inhibitor. Dialysis should be stopped immediately if symptoms such as nausea, abdominal cramps, burning, angioedema, shortness of breath and severe hypotension occur. Symptoms are not relieved by antihistamines. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agents.

Anaphylactoid Reactions during Desensitization: There have been isolated reports of patients experiencing sustained life threatening anaphylactoid reactions while receiving ACE inhibitors during desensitization treatment with hymenoptera (bees, wasps) venom. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld for at least 24 hours, but they have reappeared upon inadvertent rechallenge.

Hyperkalemia and Potassium-Sparing Diuretics: Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials treated with ALTACE. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was not a cause of discontinuation of therapy in any hypertensive patient. Risk factors for the development of hyperkalemia may include renal insufficiency, diabetes mellitus, and the concomitant use of agents to treat hypokalemia or other drugs associated with increases in serum potassium (see PRECAUTIONS – Drug Interactions).

Surgery/Anesthesia: In patients undergoing surgery or anesthesia with agents producing hypotension, ALTACE may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it may be corrected by volume repletion.

Aortic Stenosis: There is concern, on theoretical grounds, that patients with aortic stenosis might be at particular risk of decreased coronary perfusion when treated with vasodilators because they do not develop as much afterload reduction.

Patients with Impaired Liver Function: Hepatitis (hepatocellular and/or cholestatic), elevations of liver enzymes and/or serum bilirubin have occurred during therapy with ACE inhibitors in patients with or without pre-existing liver abnormalities. In most cases the changes were reversed on discontinuation of the drug. Elevations of liver enzymes and/or serum bilirubin have been reported with ALTACE (see ADVERSE REACTIONS). Should the patient receiving ALTACE experience any unexplained symptoms particularly during the first weeks or months of treatment, it is recommended that a full set of liver function tests and any other necessary investigations be carried out. Discontinuation of ALTACE should be considered when appropriate.

There are no adequate studies in patients with cirrhosis and/or liver dysfunction. ALTACE should be used with particular caution in patients with pre-existing liver abnormalities. In such patients baseline liver function tests should be obtained before administration of the drug and close monitoring of response and metabolic effects should apply.

Nursing Mothers: Ingestion of a single 10 mg oral dose of ALTACE resulted in undetectable amounts of ramipril and its metabolites in breast milk. However, because multiple doses may produce low milk concentrations that are not predictable from single doses, ALTACE should not be administered to nursing mothers.

Pediatric Use: The safety and effectiveness of ALTACE in children have not been established; therefore use in this age group is not recommended.

Use in Elderly: Although clinical experience has not identified differences in response between the elderly (>65 years) and younger patients, greater sensitivity of some older individuals cannot be ruled out (see FULL PRODUCT MONOGRAPH, Pharmacokinetics and Metabolism).

Patient Alertness: ALTACE may lower the state of patient alertness and/or reactivity, particularly at the start of treatment (see ADVERSE REACTIONS).

Cough: A dry, persistent cough, which usually disappears only after withdrawal or lowering of the dose of ALTACE, has been reported. Such possibility should be considered as part of the differential diagnosis of cough.

Drug Interactions: Diuretic therapy: Hypotension may result but can be minimized by discontinuing diuretic or increasing salt intake prior to ramipril treatment and/or reduce initial dose. **Agents increasing serum potassium:** Use potassium sparing diuretics with caution and monitor frequently. **Agents causing renin release:** ALTACE antihypertensive effect increased. **Lithium:** Lithium levels may be increased. Administer lithium with caution and monitor levels frequently. **Antacids:** The bioavailability of ALTACE and the pharmacokinetics of ramiprilat were not affected. **Digoxin:** No change in ramipril, ramiprilat or digoxin serum levels. **Acenocoumarol:** No significant changes. **Non-steroidal anti-inflammatory agents (NSAID):** The antihypertensive effects of ACE inhibitors may be reduced with concomitant administration of NSAIDs.

ADVERSE REACTIONS: Serious adverse events occurring in North American controlled clinical trials with ALTACE monotherapy in hypertension (n=972) were: hypotension (0.1%); myocardial infarction (0.3%); cerebrovascular accident (0.1%); edema (0.2%); syncope (0.1%). Among all North American ALTACE patients (n=1244), angioedema occurred in patients treated with ALTACE and a diuretic (0.1%).

The most frequent adverse events occurring in North American placebo-controlled clinical trials with ALTACE monotherapy in hypertensive patients (n=651) were: headache (15.1%); dizziness (3.7%); asthenia (3.7%); chest pain (2.0%); nausea (1.8%); peripheral edema (1.8%); somnolence (1.7%); impotence (1.5%); rash (1.4%); arthritis (1.1%); dyspnea (1.1%). Discontinuation of therapy due to clinical adverse events was required in 5 patients (0.8%).

In placebo-controlled trials, an excess of upper respiratory infection and flu syndrome was seen in the ramipril group. As these studies were carried out before the relationship of cough to ACE inhibitors was recognized, some of these events may represent ramipril-induced cough. In a later 1-year study, increased cough was seen in almost 12% of ALTACE patients, with about 4% of these patients requiring discontinuation of treatment. Approximately 1% of patients treated with ALTACE monotherapy in North American controlled clinical trials (n=972) have required discontinuation because of cough.

Clinical Laboratory Test Findings: Increased creatinine; increases in blood urea nitrogen (BUN); decreases in hemoglobin or hematocrit; elevations of liver enzymes, serum bilirubin, uric acid, blood glucose; leukopenia, eosinophilia, proteinuria.

DOSAGE AND ADMINISTRATION: Dosage of ALTACE (ramipril) must be individualized. Initiation of therapy requires consideration of recent antihypertensive drug treatment, the extent of blood pressure elevation and salt restriction. The dosage of other antihypertensive agents being used with ALTACE may need to be adjusted.

Monotherapy: The recommended initial dosage of ALTACE in patients not on diuretics is 2.5 mg once daily. Dosage should be adjusted according to blood pressure response, generally, at intervals of at least two weeks. The usual dose range is 2.5 to 10 mg once daily. A daily dose of 20 mg should not be exceeded.

In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval. This can be evaluated by measuring blood pressure just prior to dosing to determine whether satisfactory control is being maintained for 24 hours. If it is not, either twice daily administration with the same total daily dose, or an increase in dose should be considered. If blood pressure is not controlled with ALTACE alone, a diuretic may be added. After the addition of a diuretic, it may be possible to reduce the dose of ALTACE.

Concomitant Diuretic Therapy: Symptomatic hypotension occasionally may occur following the initial dose of ALTACE and is more likely in patients who are currently being treated with a diuretic. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with ALTACE to reduce the likelihood of hypotension (see WARNINGS). If the diuretic cannot be discontinued, an initial dose of 1.25 mg ALTACE should be used with careful medical supervision for several hours and until blood pressure has stabilized. The dosage of ALTACE should subsequently be titrated (as described above) to the optimal response.

Use in Renal Impairment: For patients with a creatinine clearance below 40 mL/min/1.73m² (serum creatinine above 2.5 mg/dL), the recommended initial dose is 1.25 mg ALTACE once daily. Dosage may be titrated upward until blood pressure is controlled or to a maximum total daily dose of 5 mg. In patients with severe renal impairment (creatinine clearance below 10 mL/min/1.73m²) the maximum dose of 2.5 mg ALTACE should not be exceeded.

AVAILABILITY: No. 4 hard gelatin capsules:
- 1.25 mg (white/yellow);
- 2.5 mg (white/orange);
- 5 mg (white/red);
- 10 mg (white/blue).

ALTACE capsules 1.25 mg, 2.5 mg, 5 mg and 10 mg are packaged in cartons of 30 (2 x 15 blister-packed) capsules.

Product monograph available upon request.

REFERENCES: 1. Todd PA, Benfield P. *Drugs* 39(1):10-135, 1990. 2. Schreiner M, et al. *J Cardiovasc Pharmacol* 18(2):S137-S140, 1991. 3. Marre M, et al. *J Cardiovasc Pharmacol* 18(2):S165-S168, 1991. 4. Hirata Y, et al. *Cur Ther Research* 45(6):967-974, 1989. 5. Altace Product Monograph. 6. Al Nahhas AM, et al. *Nephron* 54;47-52, 1990. 7. Competitive Product Monographs.

Hoechst-Roussel Canada Inc.
Montreal, Quebec BPIALT96009
MEMBER PMAC PAAB

PRESCRIBING INFORMATION

NICODERM®

Nicotine transdermal system
Smoking Cessation Aid

ACTIONS

Nicoderm (nicotine transdermal system) is a multilayered rectangular film containing nicotine as the active ingredient. It provides 24 hour rate-controlled delivery of nicotine following its application to intact skin. Nicoderm reduces the withdrawal symptoms associated with smoking cessation and thus increases the success rate of smoking cessation programs.

INDICATIONS AND CLINICAL USE

Nicoderm (nicotine transdermal system) is indicated as an aid to smoking cessation for partial relief of nicotine withdrawal symptoms. Nicoderm treatment should be used as part of a comprehensive behavioral smoking-cessation program.

CONTRAINDICATIONS

Nicoderm is contraindicated:
1. In patients with hypersensitivity or allergy to nicotine or the components of the transdermal system. Patients with acute hypersensitivity reactions should discontinue use of Nicoderm and should be advised of the possibility of acute hypersensitivity reactions to other forms of nicotine, including cigarettes; **2.** In non-smokers or occasional smokers; **3.** In children **4.** In patients during the immediate post-myocardial infarction period, in patients with life-threatening arrhythmias, in patients with severe or worsening angina pectoris and in patients who have had a recent cerebral vascular accident **5.** In pregnant women **6.** In nursing mothers, and **7.** In patients with generalized skin disorders.

WARNINGS

Nicotine from any source can be toxic and addictive. The amounts of nicotine that are tolerated by adult smokers can produce symptoms of poisoning and could prove fatal if the Nicoderm system is applied or ingested by children or pets. Used Nicoderm systems contain approximately 70% of their initial drug content. Therefore, patients should be cautioned to keep both the used and unused Nicoderm systems out of the reach of children and pets.

Cardiovascular or Peripheral Vascular Disease

The risks of nicotine replacement in patients with certain cardiovascular and peripheral vascular diseases should be weighed against the benefits of including nicotine replacement in a smoking-cessation program for them. Specifically, patients with coronary heart disease (history of myocardial infarction and/or angina pectoris), serious cardiac arrhythmias, or vasospastic diseases (Buergers disease, Prinzmetal's variant angina) should be carefully screened and evaluated before nicotine replacement is prescribed.

Tachycardia occurring in association with the use of Nicoderm therapy has been reported occasionally. If serious cardiovascular symptoms occur with the use of Nicoderm therapy, it should be discontinued.

PRECAUTIONS

General

The patient should be urged to stop smoking completely when initiating Nicoderm (nicotine transdermal system) therapy (see **DOSAGE AND ADMINISTRATION**). Patients should be informed that if they continue to smoke while using Nicoderm systems, they may experience adverse effects due to peak nicotine levels higher than those experienced from smoking alone. If there is a clinically significant increase in cardiovascular or other effects attributable to nicotine, the Nicoderm dose should be reduced or Nicoderm treatment discontinued (see **WARNINGS**). The use of Nicoderm systems beyond 3 months by patients who stop smoking should be discouraged. If the patient continues to smoke, treatment should be discontinued after 4 weeks.

Pregnancy

Women of childbearing age should be advised to take adequate precautions to avoid becoming pregnant while using Nicoderm. Nicoderm therapy should be discontinued if pregnancy is suspected. (see CONTRAINDICATIONS)

Drug Interactions

Physicians should anticipate that the pharmacokinetics of certain concomitant medications may be altered by smoking cessation with or without nicotine replacement. Therefore the dosage of certain concomitant medications may require adjustment.

May require a decrease in dose at cessation of smoking	**Possible Mechanism**
Acetaminophen, caffeine, imipramine, oxazepam, pentazocine, propranolol, theophylline	Deinduction of hepatic enzymes on smoking cessation
Insulin	Increase in subcutaneous insulin absorption with smoking cessation
Adrenergic antagonists (eg. prazosin, labetalol)	Decrease in circulating catecholamines with smoking cessation
May require an increase in dose at cessation of smoking	**Possible Mechanism**
Adrenergic agonist (eg. isoproteranol, phenylephrine)	Decrease in circulating catecholamines with smoking cessation

Allergic Reactions

Patients should be instructed to promptly discontinue the use of Nicoderm systems and contact their physicians if they experience severe or persistent local skin reactions (eg. severe erythema, pruritus, or edema) at the site of application or a generalized skin reaction (eg. urticaria, hives, or generalized rash). Patients using Nicoderm therapy concurrently with other transdermal systems may exhibit local reactions at both application sites. In such patients use of one or both systems may have to be discontinued.

Skin Disease

Nicoderm systems are usually well tolerated by patients with normal skin, but may be irritating for patients with some skin disorders (atopic or eczematous dermatitis).

Renal or Hepatic Insufficiency

The pharmacokinetics of nicotine have not been studied in the elderly or in patients with renal or hepatic impairment; however, given that nicotine is extensively metabolized and that its total system clearance is dependent on liver blood flow, some influence of hepatic impairment on drug kinetics (reduced clearance) should be anticipated. Only severe renal impairment would be expected to affect the clearance of nicotine or its metabolites from the circulation.

Endocrine Diseases

Nicoderm therapy should be used with caution in patients with hyperthyroidism, pheochromocytoma, or insulin-dependent diabetes since nicotine causes the release of catecholamines by the adrenal medulla.

Peptic Ulcer Disease

Nicotine delays healing in peptic ulcer disease; therefore, Nicoderm therapy should be used with caution in patients with active peptic ulcers and only when the benefits of including nicotine replacement in a smoking-cessation program outweigh the risks.

Accelerated Hypertension

Nicotine therapy constitutes a risk factor for development of malignant hypertension in patients with accelerated hypertension; therefore, Nicoderm therapy should be used with caution in these patients and only when the benefits of including nicotine replacement in a smoking-cessation program outweigh the risks.

Use in Children and the Elderly

Nicoderm therapy is not recommended for use in children, because its safety and effectiveness in children and adolescents who smoke has not been evaluated. In clinical trials Nicoderm therapy appeared to be as effective in the over 60 age group as in younger adult smokers. However, asthenia, various body aches and dizziness occurred slightly more often in patients over 60 years of age.

Drug Dependency

Nicoderm therapy is likely to have a low abuse potential based on differences between it and cigarettes in four characteristics commonly considered important in contributing to abuse: much slower absorption, much smaller fluctuations in blood levels, lower blood levels of nicotine, and less frequent use (i.e., once daily).

Dependence on nicotine polacrilex chewing gum replacement therapy has been reported. Such dependence might also occur from transference to Nicoderm systems of tobacco-based nicotine dependence. The use of the system beyond 3 months has not been evaluated and should be discouraged. To minimize the risk of dependence, patients should be encouraged to withdraw gradually from Nicoderm treatment after 4 to 8 weeks of use. Recommended dose reduction is to progressively decrease the dose every 2 to 4 weeks (see **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

Assessment of adverse events in patients who participated in controlled clinical trials is complicated by the occurrence of GI and CNS effects of nicotine withdrawal as well as nicotine excess. The actual incidence of both are con-founded by concurrent smoking by many of the patients. When reporting adverse events in the clinical trials, the clinical investigators did not attempt to identify the cause of the symptom.

The most common adverse event associated with Nicoderm (nicotine transdermal system) is a short-lived erythema, pruritus, and/or burning at the application site, which was seen at least once in 47% of patients on the Nicoderm system in the clinical trials. Local erythema after system removal was noted at least once in 14% of patients and local edema in 3%. Erythema generally resolved within 24 hours. Cutaneous hypersensitivity (contact sensitization) occurred in 2% of patients on Nicoderm systems (see **PRECAUTIONS**).

The following table presents the number of patients reporting adverse events at a frequency greater than 1% in a placebo-controlled clinical trial involving 375 patients who used Nicoderm and 128 patients who used placebo.

	Number (%) of Patients Reporting Adverse Events	
	NICODERM	**PLACEBO**
CARDIOVASCULAR SYSTEM		
Vasodilatation	5 (1.3%)	1 (0.8%)
Tachycardia	5 (1.3%)	0 (0%)
DIGESTIVE SYSTEM		
Abdominal pain	8 (2.1%)	4 (3.1%)
Dyspepsia	21 (5.6%)	5 (3.9%)
Nausea	18 (4.8%)	1 (0.8%)
Diarrhea	9 (2.4%)	2 (1.6%)
Constipation	7 (1.9%)	3 (2.3%)
Dry mouth	6 (1.6%)	0 (0%)
Flatulence	5 (1.3%)	2 (1.6%)
Vomiting	5 (1.3%)	1 (0.8%)
Taste perversion	7 (1.9%)	3 (2.3%)
MUSCULOSKELETAL SYSTEM		
Myalgia	10 (2.7%)	0 (0%)
NERVOUS SYSTEM		
Headache	69 (18.4%)	29 (22.6%)
Asthenia	17 (4.5%)	3 (2.3%)
Insomnia	56 (14.9%)	11 (8.6%)
Abnormal dreams	28 (7.5%)	1 (0.8%)
Dizziness	27 (7.2%)	3 (2.3%)
Depression	10 (2.7%)	6 (4.7%)
Somnolence	5 (1.3%)	2 (1.6%)
Nervousness	6 (1.6%)	1 (0.8%)
Hypertonia	5 (1.3%)	0 (0%)
RESPIRATORY SYSTEM		
Increased cough	11 (2.9%)	1 (0.8%)
Pharyngitis	6 (1.6%)	2 (1.6%)
SKIN		
Rash	7 (1.9%)	2 (1.6%)
Sweating	5 (1.3%)	0 (0%)
BODY AS A WHOLE		
Pain	8 (2.1%)	1 (0.8%)
Flu syndrome	11 (2.9%)	1 (0.8%)
Muscle ache	7 (1.9%)	0 (0%)
Tingling	22 (5.9%)	0 (0%)
Soreness	5 (1.3%)	0 (0%)
Warmth	8 (2.1%)	1 (0.8%)

DOSAGE AND ADMINISTRATION

Patients must desire to stop smoking and should be instructed to stop smoking immediately as they begin using Nicoderm therapy. The patient should read the patient instruction sheet on Nicoderm therapy and be encouraged to ask questions.

Therapy should begin with the Nicoderm 21 mg/day system and continue for 6 weeks. The patient should stop smoking cigarettes completely during this period. If the patient is unable to stop smoking within 4 weeks, Nicoderm therapy should be stopped, since few additional patients in clinical trials were able to quit after this time. Patients who have successfully abstained from smoking should have their dose of Nicoderm reduced after 6 weeks of treatment. Treatment with Nicoderm 14 mg/day should then be initiated for 2 weeks followed by 2 weeks on Nicoderm 7 mg/day.

For patients who have cardiovascular disease, weigh less than 45 kg or who smoke less than 1/2 pack of cigarettes a day, treatment should be started with Nicoderm 14 mg/day for 6 weeks. The dose should then be decreased to Nicoderm 7 mg/day for the final 2-4 weeks of treatment.

In all patients the need for dosage adjustment should be assessed during the first two weeks of therapy. The entire course of nicotine replacement and gradual withdrawal should take 8-12 weeks, depending on the size of the initial dose.

As the use of Nicoderm beyond 3 months has not been studied, this duration of treatment should not be exceeded.

The Nicoderm system should be applied promptly upon its removal from the protective pouch to prevent evaporative loss of nicotine from the system. Nicoderm systems should be used only when the pouch is intact to assure that the product has not been tampered with.

Nicoderm systems should be applied only once a day to a non-hairy, clean, dry skin site on the upper body or outer upper arm. After 24 hours, the used Nicoderm system should be removed and a new system applied to an alternate skin site. Skin sites should not be reused for at least a week. Patients should be cautioned not to continue to use the same system for more than 24 hours.

AVAILABILITY OF DOSAGE FORMS

Nicoderm systems are labelled by the dose actually absorbed by the patient.

Nicoderm 21 mg/day: Each rectangular 22 cm^2 system contains 114 mg of nicotine and provides 24 hour rate-controlled delivery of 21 mg/day to the patient. Available in boxes of 14 systems.

Nicoderm 14 mg/day: Each rectangular 15 cm^2 system contains 78 mg of nicotine and provides 24 hour rate-controlled delivery of 14 mg/day to the patient. Available in boxes of 14 systems.

Nicoderm 7 mg/day: Each rectangular 7 cm^2 system contains 36 mg of nicotine and provides 24 hour rate-controlled delivery of 7 mg/day to the patient. Available in boxes of 14 systems.

Product Monograph available on request.

MARION MERRELL DOW
CANADA
Laval, Quebec H7L 4A8

MNDJRN0294325

MONISTAT*

MICONAZOLE NITRATE

When *you* know it's vaginal candidiasis. When *she* knows it, too.

PRESCRIBING INFORMATION

MONISTAT* 7 Cream (miconazole nitrate 2%)

MONISTAT* 7 Vaginal Suppositories
(miconazole nitrate 100 mg)

MONISTAT* 7 DUAL-PAK*
(miconazole nitrate 100 mg/2%)

MONISTAT* 3 Vaginal Ovules
(miconazole nitrate 400 mg)

MONISTAT* 3 DUAL-PAK*
(miconazole nitrate 400 mg/2%)

MONISTAT* Derm Cream (miconazole nitrate 2%)

CLASSIFICATION: Antifungal

INDICATIONS AND CLINICAL USE:
MONISTAT 7 Vaginal Cream, MONISTAT 7 Vaginal Suppositories and MONISTAT 3 Vaginal Ovules are indicated for the local treatment of vulvovaginal candidiasis (moniliasis). MONISTAT 7 DUAL-PAK and MONISTAT 3 DUAL-PAK are indicated for the local treatment of vulvovaginal candidiasis (moniliasis) and for the relief of particularly severe external itching and irritation associated with vulvovaginal candidiasis.

Although vulvovaginal candidiasis may be more difficult to cure during pregnancy, pregnant patients can be treated with the same regimen as non-pregnant patients. The 3-day regimen is preferred, with the 7-day regimen providing an effective alternative.

No significant difference in therapeutic cure rate (therapeutic cure includes both symptomatic and microbiological cure) was reported between the pregnant and non-pregnant patient groups who participated in clinical evaluations of the 3-day (ovules) or 7-day (suppositories + cream) treatment regimens.

Similarly, users and non-users of oral contraceptives who participated in these clinical evaluations experienced therapeutic cure rates which did not differ significantly.

In addition, no statistically significant differences in therapeutic cure rates were noted between patients undergoing dosage regimens of varying duration (3, 7, 10, and 14 day).

MONISTAT Derm Cream is indicated for the topical treatment of dermatophytes and Candida infections and also lesions caused by mixed infections involving susceptible fungi. It is used clinically in conjunction with vaginal ovules or suppositories in MONISTAT 3 and 7 DUAL-PAKs, respectively, when symptoms of vulvovaginal candidiasis are particularly extensive.

CONTRAINDICATIONS:
Patients known to be hypersensitive to this drug.

PRECAUTIONS:

1. Patients should not use MONISTAT vaginal preparations for self-medication if vaginal pruritus or discomfort is occurring for the first time. In this instance, a physician must be consulted to establish the diagnosis of vulvovaginal candidiasis.

2. Patients should not use MONISTAT vaginal preparations for self-medication if abdominal pain, fever or malodorous vaginal discharge are present, as a condition more serious than vulvovaginal candidiasis may exist.

3. Patients should be advised to discontinue medication if sensitization or other signs of irritation (rash, burning, blistering, redness) not present before therapy occur.

4. Intractable candidiasis may be the presenting symptom of unrecognized diabetes; thus appropriate urine/blood studies may be indicated in patients not responding to treatment. In any case, if a patient is unresponsive to therapy appropriate microbiological studies should be repeated to confirm the diagnosis of vulvovaginal candidiasis and to rule out other pathogens.

5. Pregnant patients should be advised either to exercise caution in the use of the vaginal applicator for the cream or the suppository or to insert the suppository digitally.

6. Follow-up reports on infants born to twenty-six pregnant patients who participated in European and North American clinical evaluations of Miconazole Nitrate 100 mg Suppositories and infants born to 167 of 263 pregnant patients (some follow-up reports are not yet available) who participated in North American clinical evaluations of Miconazole Nitrate 2% Cream administered in a 14-day regimen described no complications or adverse effects attributed to this therapeutic agent. Nevertheless, since miconazole nitrate is absorbed in small amounts from the human vagina, MONISTAT vaginal preparations should not be used by pregnant or nursing women unless the physician considers it essential to the welfare of the patient.

7. During therapy it may be advisable to instruct the patient to abstain from intercourse.

8. Concurrent use of the suppository or ovule with natural rubber products such as vaginal diaphragms or condoms is not recommended.

9. Avoid introducing MONISTAT Derm Cream into the eyes.

ADVERSE REACTIONS:

In general, the complaints reported with miconazole nitrate therapy involved vulvovaginal burning, itching, irritation, and edema as well as hives.

A total of 1,089 patients participated in international clinical evaluations of Miconazole Nitrate formulated as the 2% Cream and administered in dosage regimens of varying duration. Of these, fifty-nine patients reported reactions which were possibly drug related but not severe enough to cause discontinuation of therapy, four patients discontinued therapy due to vulvovaginal burning and itching, and one patient discontinued therapy due to hives.

A total of 1,724 patients participated in international clinical evaluations of Miconazole Nitrate formulated as the 100 mg Suppository and administered in dosage regimens of varying duration. Of these, three patients reported reactions which were interpreted as minor treatment emergent signs and symptoms (burning, itching, edema) and considered by the investigators to be non-therapy related. No patients were reported to have discontinued therapy due to drug related reasons.

The three-day treatment with MONISTAT 400 mg Vaginal Ovules was exceptionally well tolerated by a total of 410 patients in three clinical studies, without any related side effects. However, the generally reported complaints referred to above could be expected with this dosage form and regimen as well.

The MONISTAT DUAL-PAK products combine a small amount (9 gram) of miconazole nitrate cream (MONISTAT Derm) to be applied externally during a course of therapy with MONISTAT 7 Vaginal Suppositories or MONISTAT 3 Vaginal Ovules so a similar safety and efficacy profile as with each individually could be expected.

On rare occasions it has been reported that patients treated with MONISTAT Derm Cream experienced mild pruritus, irritation and burning at the site of application.

DOSAGE AND ADMINISTRATION:

Cream and Suppository: One 5 g applicatorful of MONISTAT 7 Vaginal Cream (equivalent to 100 mg miconazole nitrate) or 100 mg suppository administered intravaginally once daily at bedtime for 7 consecutive days.

Ovule: One 400 mg ovule administered intravaginally once daily at bedtime for 3 consecutive days.

A course of therapy with the cream, suppository or ovule may be repeated if the patient remains symptomatic and if it has been determined by appropriate smears and cultures that the infecting organism is still miconazole susceptible Candida.

Dual-Paks: (To be used when symptoms are particularly extensive.) One 100 mg suppository or one 400 mg ovule administered intravaginally once daily at bedtime for 7 (MONISTAT 7) or 3 (MONISTAT 3) consecutive days, respectively. Apply a thin layer of the cream to external areas twice daily, in the morning and evening. Massage gently until the cream disappears. **Also known as Combination Packs.**

MONISTAT Derm Cream: Apply sufficient cream to cover the affected area twice daily; morning and evening. Massage gently until cream disappears. Early clinical improvement (1-2 weeks) has been seen in the treatment of infections caused by dermatophytes and Candida species and in mixed fungal infections, but resistant lesions may take longer to clear. Candida infections should be treated for two weeks and dermatophyte infections for one month in order to reduce the possibility of recurrence. If a patient shows no clinical improvement after 30 days of treatment, the diagnosis should be reconsidered.

AVAILABILITY OF DOSAGE FORMS:

MONISTAT 7 Vaginal Cream (miconazole nitrate 2%): is available in individual packages each containing a 45 g tube of cream sufficient for one 7-day course of therapy and seven ORTHO* Disposable Applicators.

MONISTAT 7 Vaginal Suppositories (miconazole nitrate 100 mg) are available in boxes containing a vaginal suppository applicator and seven suppositories, each sealed in an opaque polyvinylchloride mould. This represents sufficient drug for one 7-day course of therapy.

MONISTAT 3 Vaginal Ovules (miconazole nitrate 400 mg) are available in individual packages each containing three ovules sufficient for one 3-day course of therapy and a vaginal applicator.

MONISTAT 7 DUAL-PAK: Each package contains seven MONISTAT 7 Vaginal Suppositories (miconazole nitrate 100 mg) sufficient for one 7-day course of therapy, a vaginal applicator and a 9 g tube of MONISTAT Derm Cream (miconazole nitrate 2%). **Also referred to as MONISTAT 7 Combination Pack.**

MONISTAT 3 DUAL-PAK: Each package contains three MONISTAT 3 Vaginal Ovules (miconazole nitrate 400 mg) sufficient for one 3-day course of therapy, a vaginal applicator and a 9 g tube of MONISTAT Derm Cream (miconazole nitrate 2%). **Also referred to as MONISTAT 3 Combination Pack.**

MONISTAT Derm Cream is supplied as 2% miconazole nitrate cream in 15 gram and 30 gram tubes

Product Monograph is available upon request.

McNEIL CONSUMER PRODUCTS COMPANY
Guelph, Canada N1K 1A5

January 1995

PAAB
CCPP

Tri-Cyclen*

0.180 mg., 0.215 mg. and 0.250 mg. norgestimate 0.035 mg. ethinyl estradiol

Tablets with Norgestimate

TRI-CYCLEN* Tablets / **CYCLEN*** Tablets (norgestimate and ethinyl estradiol)

PHARMACOLOGICAL CLASSIFICATION Synthetic steroidal combination oral contraceptives.

ACTION The primary mechanism of action of CYCLEN Tablets and TRI-CYCLEN Tablets is inhibition of ovulation. Other effects caused by treatment (i.e., alteration of the endometrium and thickening of cervical mucus), appear to interfere with implantation and conception.

INDICATION CYCLEN Tablets and TRI-CYCLEN Tablets are indicated for conception control.

CONTRAINDICATIONS 1. History of/or actual thrombophlebitis or thromboembolic disorders. **2.** History of/or actual cerebrovascular disorders. **3.** History of/or actual myocardial infarction or coronary arterial disease. **4.** Active liver disease or history of/or actual benign or malignant liver tumours. **5.** Known or suspected carcinoma of the breast. **6.** Known or suspected estrogen-dependent neoplasia. **7.** Undiagnosed abnormal vaginal bleeding. **8.** Any ocular lesion arising from ophthalmic vascular disease, (i.e., partial or complete loss of vision or defect in visual fields). **9.** Suspected or diagnosed pregnancy.

WARNINGS 1. Predisposing factors for coronary artery diseases. Cigarette smoking increases the risk of serious cardiovascular side effects and mortality. Birth control pills increase this risk, especially with increasing age. Data are available to support an upper age of 35 years for use in women who smoke. Other women independently at high risk for cardiovascular disease include those with diabetes, hypertension, abnormal lipid profile, or a family history of these. Whether oral contraceptives accentuate this risk is unclear. In low risk, non-smoking women of any age, the benefits of oral contraceptive use outweigh the possible cardiovascular risks associated with low dose formulations. Oral contraceptives may be prescribed for these women up to menopause.

Cigarette smoking increases the risk of serious adverse effects on the heart and blood vessels. The risk increases with age and becomes significant in oral contraceptive users over 35 years of age. Women should be counselled not to smoke.

2. Discontinue medication at the earliest manifestation of: A. Thromboembolic and Cardiovascular Disorders such as: Thrombophlebitis, pulmonary embolism, cerebrovascular disorders, myocardial ischemia, mesenteric thrombosis, and retinal thrombosis. B. Conditions which predispose to venous stasis and to vascular thrombosis, e.g. immobilization after accidents or long-term confinement to bed. Other non-hormonal contraceptives should be used until regular activities are resumed. For use of oral contraceptives when surgery is contemplated, see PRECAUTIONS. C. Visual Defects, Partial or Complete. D. Papilledema, or Ophthalmic Vascular Lesions. E. Severe Headache of Unknown Etiology or Worsening of Pre-existing Migraine Headache.

PRECAUTIONS 1. Physical examination and follow-up before use, a thorough history and physical examination should be performed, including blood pressure determination. Breasts, liver, extremities, and pelvic organs should be examined. A Papanicolaou smear should be taken if patient has been sexually active. The first follow-up visit should be done 3 months after oral contraceptives are prescribed and thereafter, at least once a year, or more. Each annual examination should include those procedures that were done at initial visit as outlined above or per recommendations of the Canadian Task Force on the Periodic Health Examination. **2. Pregnancy** Oral contraceptives should not be taken by pregnant women. If conception occurs while taking the pill, there is no conclusive evidence that the estrogen and progestin contained in the oral contraceptive will damage the developing child. **3. Breastfeeding** In breast-feeding women, the use of oral contraceptives results in the hormonal components being excreted in breast milk and may reduce its quantity and quality. If the use of oral contraceptives is initiated after the establishment of lactation, there does not appear to be any effect on the quantity and quality of the milk. There is no evidence that low dose oral contraceptives are harmful to the nursing infant. **4. Hepatic Function** Patients who have had jaundice or a history of cholestatic jaundice during pregnancy should be given oral contraceptives with great care and under close observation. The development of severe generalized pruritus or icterus requires that the medication be withdrawn until the problem is resolved. If the jaundice should prove to be cholestatic in type, the use of oral contraceptives should not be resumed. In patients taking oral contraceptives, changes in the composition of the bile may occur and an increased incidence of gallstones has been reported. Hepatic nodules (adenoma and focal nodular hyperplasia) have been reported, particularly in long-term users of oral contraceptives. Although these lesions are extremely rare they have caused fatal intra-abdominal hemorrhage and should be considered in women presenting with an abdominal mass, acute abdominal pain, or evidence of intra-abdominal bleeding. **5. Hypertension Patients** with essential hypertension whose blood pressure is well-controlled may be given oral contraceptives under close supervision. If a significant elevation of blood pressure in previously normotensive or hypertensive subjects occurs at any time during administration, cessation of medication is necessary. **6. Migraine and Headache** The onset or exacerbation of migraine or the development of headache of a new pattern which is recurrent, persistent or severe, requires discontinuation of oral contraceptives and evaluation of the cause. **7. Diabetes** Current low dose oral contraceptives exert minimal impact on glucose metabolism. Diabetic patients, or those with a family history of diabetes, should be observed closely to detect worsening of carbohydrate metabolism. Patients predisposed to diabetes who can be kept under close supervision may be given oral contraceptives. Young diabetic patients whose disease is of recent origin, well-controlled, and not associated with hypertension or other signs of vascular disease such as ocular fundal changes, should be monitored more frequently while using oral contraceptives. **8. Ocular Disease Patients** who are pregnant or are taking oral contraceptives, may experience corneal edema that may cause visual disturbances and changes in tolerance to contact lenses, especially of the rigid type. Soft contact lenses usually do not cause disturbances. If visual changes or alterations in tolerance to contact lenses occur, temporary or permanent cessation of wear may be advised. **9. Breasts** Increasing age and a strong family history are the most significant risk factors for the development of breast cancer. Other established risk factors include obesity, nulliparity and late age at first full-term pregnancy. Women that may be at increased risk of developing breast cancer before menopause are long-term users of oral contraceptives (more than 8 years) and starters at early age. In few women, the use of oral contraceptives may accelerate the growth of an existing but undiagnosed breast cancer. Since any potential increased risk related to oral contraceptive use is small, there is no reason to change prescribing habits. Women receiving oral contraceptives should be instructed in self-examination of their breasts. Their physicians should be notified whenever any masses are detected. Annual breast examination are also recommended because, if a breast cancer should develop, estrogen-containing drugs may cause a rapid progression. **10. Vaginal Bleeding** Persistent irregular vaginal bleeding requires assessment to exclude underlying pathology. **11. Fibroids** Patients with fibroids (leiomyomata) should be carefully observed. Sudden enlargement, pain, or tenderness require discontinuation. **12. Emotional Disorders** Patients with a history of emotional disturbances, especially the depressive type, may be more prone to have a recurrence of depression while taking oral contraceptives. In cases of a serious recurrence, a trial of an alternate method of contraception should be made which may help to clarify the possible relationship. Women with premenstrual syndrome (PMS) may have a varied response to oral contraceptives, ranging from symptomatic improvement to worsening of the condition. **13. Laboratory** Tests Results of laboratory tests should be interpreted in light of the patient's oral contraceptive use. The following laboratory tests are modified. A. Liver function tests Aspartate serum transaminase (AST) - variously reported elevations. Alkaline phosphatase and gamma glutamine transaminase (GGT) - slightly elevated. B. Coagulation tests Minimal elevation of test values reported for such parameters as prothrombin and Factors VII, VIII, IX and X. C. Thyroid function tests Protein binding of thyroxine is increased as indicated by increased total serum thyroxine concentrations and decreased T3 resin uptake. D. Lipoproteins Small changes of unproven clinical significance may occur in lipoprotein cholesterol fractions. E. Gonadotropins LH and FSH levels are suppressed by the use or oral contraceptives. Wait two weeks after discontinuing the use of oral contraceptives before measurements are made. **14. Tissue Specimens** Pathologists should be advised of oral contraceptive therapy when specimens obtained from surgical procedures and Pap Smears submitted for examination. **15. Return to Fertility** After discontinuing therapy, the patient should delay pregnancy until at least one spontaneous menstrual cycle has occurred in order to date the pregnancy. An alternative contraceptive method should be used during this time. **16. Amenorrhea** Women having a history of oligomenorrhea, secondary amenorrhea, or irregular cycles may remain anovulatory or become amenorrheic following discontinuation of estrogen-progestin combination therapy. Amenorrhea, especially if associated with breast secretion, that continues for 6 months or more after withdrawal, warrants a careful assessment of hypothalamic-pituitary function. **17. Thromboembolic Complications** - Post-surgery There is an increased risk of post-surgery thromboembolic complications in oral contraceptive users after major surgery. If feasible, oral contraceptives should be discontinued and an alternative method substituted at least one month prior to **MAJOR** elective surgery. Oral contraceptives should not be resumed until the first menstrual period after hospital discharge following surgery. **18. Drug Interactions** The concurrent administration of oral contraceptives with other drugs may result in an altered response to either agent. Reduced effectiveness of the oral contraceptive, should it occur, is more likely with low dose formulations. It is important to ascertain all drugs that a patient is taking, both prescription and non-prescription.

Drugs Which May Decrease The Efficacy of Oral Contraceptives -

Anti-convulsants: carbamazepine, ethosuximide, phenobarbital, phenytoin, primidone. Induction of hepatic microsomal enzymes:Rapid metabolism of estrogen and increased binding of progestin and ethinyl estradiol to SHBG. Use higher dose OCs (50 mcg ethinyl estradiol), another drug or another method. **Antibiotics:** ampicillin, cotrimoxazole, penicillin. Enterohepatic circulation disturbance, intestinal hurry. For short course, use additional method or use another drug. For long course, use another method. Rifampicin. Increased metabolism of progestins. Suspected acceleration of estrogen metabolism. Use another method. Chloramphenicol, metronidazole, neomycin, nitrofurantoin, sulfonamides, tetracyclines. Induction of hepatic microsomal enzymes. Also disturbance of enterohepatic circulation. For short course, use additional method or use another drug. For long course, use another method. Troleandomycin. May retard metabolism of OCs, increasing the risk of cholestatic jaundice. **Antifungal**: griseofulvin. Stimulation of hepatic metabolism of contraceptive steroids may occur. Use another method. **Sedatives and Hypnotics**: benzodiazepines, barbiturates, chloral hydrate, glutethimide, meprobamate. Induction of hepatic microsomal enzymes. For short course, use additiional method or another drug. For long course use another method or higher dose OCs. **Antacids**: Decreased intestinal absorption of progestins. **Other Drugs**: phenylbutazone, antihistamines, analgesics, antimigraine, preparations, Vitamin E. Reduced OC efficacy has been reported. Remains to be confirmed.

Modification of Other Drug Action by Oral Contraceptives - Alcohol: Possible increased levels of ethanol or acetaldehyde. Use with caution. **Alpha-II Adrenoreceptor Agents**: Clonidine. Sedation effect increased. Use with caution. **Anti-coagulants**: All. OCs increase clotting factors, decrease efficacy. However, OCs may potentiate action in some patients. Use another method. **Anti-convulsants**: All. Fluid retention may increase risk of seizures. Use another method. **Anti-diabetic drugs**: Oral hypoglycemics and insulin. OCs may impair glucose tolerance and increase blood glucose. Use low dose estrogen and progestin OC or another method. Monitor blood glucose. **Anti-hypertensive agents**: guanethidine and methyldopa. Estrogen component cause sodium retention, progestin has no effect. Use low estrogen OC or use another method. Beta blockers. Increased drug effect (decreased metabolism). Adjust dose of drug if necessary. Monitor cardiovascular status **Anti-pyretics**: Acetaminophen. Increased renal clearance. Dose of drug may have to be increased. Antipyridine. Impaired metabolism. Decrease dose of drug. ASA. Effects of ASA may be decreased by the short-term use of OCs. Patients on chronic ASA therapy may require an increase in ASA dosage. **Aminocaproic Acid**: Theoretically, a hypercoagulable state may occur because OCs augment clotting factors. Avoid concomitant use. Betamimetic Agents: Isoproterenol. Estrogen causes decreased response to these drugs. Adjust dose of drug as necessary. Discontinuing OCs can result in excessive drug activity. **Caffeine**: The actions of caffeine may be enhanced as OCs may impair the hepatic metabolism of caffeine. Use with caution. **Cholesterol Lowering Agents**: Clofibrate. OCs may increase the clearance of clofibrate leading to decreased levels of clofibrate. Use with caution. **Corticosteroids**: Prednisone. Markedly increased serum levels. Possible need for decrease in dose. **Cyclosporine**: May lead to an increase in cyclosporine levels and hepatotoxicity. Monitor hepatic function. The cyclosporine dose may have to be decreased. **Folic Acid**: OCs have been reported to impair folate metabolism. **Meperedine**: Possible increased analgesia and CNS depression due to decreased metabolism of meperidine. Use combination with caution. **Phenothiazine**: All phenothiazines, Estrogen potentiates the hyperprolactinemia effect of these drugs. Use other drugs or lower dose OCs. **Tranquilizers**: reserpine and similar drugs. If galactorrhea or hyperprolactinemia occurs, use another method. **Sedatives and Hypnotics**: Chlordiazepoxide, Lorazepam, Oxazepam, Diazepam. Increased effect (increased metabolism). Use with caution. **Theophylline**: All. Decreased oxidation, leading to possible toxicity. Use with caution. Monitor theophylline levels. **Tricyclic Anti-depressants**: Clomipramine (possibly others). Increased side effects; i.e, depression. Use with caution. **Vitamin B_{12}**: OCs have been reported to reduce serum levels of Vitamin B_{12}.

ADVERSE REACTIONS An increased risk of the following serious adverse reactions has been associated with the use of oral contraceptives: Thrombophlebitis, Pulmonary embolism, Mesenteric thrombosis, Neuro-ocular lesions, e.g., retinal thrombosis, Myocardial infarction, Cerebral thrombosis, Cerebral hemorrhage, Hypertension, Benign hepatic tumors, Gall bladder disease, Congenital anomalies. The following adverse reactions also have been reported: Nausea and vomiting, usually the most common adverse reaction occurs in approximately 10% or less of patients during the first cycle. Other reactions, as a general rule, are seen less frequently or only occasionally, as follows. Gastrointestinal symptoms (such as abdominal cramps and bloating), Breakthrough bleeding, Spotting, Change in menstrual flow, Dysmenorrhea, Amenorrhea during and after treatment, Temporary infertility after discontinuance of treatment, Edema, Chloasma or melasma which may persist, Breast changes: tenderness, enlargement, and secretion, Change in weight (increase or decrease), Endocervical hyperplasias, Possible diminution in lactation when given immediately post-partum, Cholestatic jaundice, Migraine, Increase in size of uterine leiomyomata, Rash (allergic), Mental depression, Reduced tolerance to carbohydrates, Vaginal candidiasis, Premenstrual-like syndrome, Intolerance to contact lenses, Change in corneal curvature (steepening), Cataracts, Optic Neuritis, Retinal thrombosis, Changes in libido, Chorea, Changes in appetite, Cystitis-like syndrome, Rhinitis, Headache, Nervousness, Dizziness, Hirsutism, Loss of scalp hair, Erythema multiform, Erythema nodosum, Hemorrhagic eruption, Vaginitis, Porphyria, Impaired renal function, Raynaud's phenomenon, Auditory disturbances, Hemolytic uremic syndrome, Pancreatitis

TREATMENT OF OVERDOSE OR ACCIDENTAL INGESTION In case of overdose or accidental ingestion by children, the physician should observe the patient closely although generally no treatment is required[2]. Gastric lavage may be utilized if considered necessary.

DOSAGE AND ADMINISTRATION TRI-CYCLEN Tablets 21 day – One Tablet daily for 3 weeks, and then take no pills for 1 week. TRI-CYCLEN Tablets 28 days– One Tablet daily. Active pills (with hormones) taken daily for 3 weeks and then 7 "reminder" pills (no hormones) taken daily for 1 week. CYCLEN Tablets 21 day – One Tablet daily for 3 weeks, and then take no pills for 1 week. CYCLEN Tablets 28 day – One Tablet daily. Active pills (with hormones) taken daily for 3 weeks and then 7 "reminder" pills (no hormones) taken daily for 1 week.

Availability CYCLEN Tablets 21-day (blue, unscored tablets with "Ortho" and "250" debossed on each side) are available in a VARIDATE* DIALPAK* Tablet Dispenser containg 21 tablets. Each blue tablet contains 0.25 mg of the progestational compound norgestimate, together with 0.035 mg of the estrogenic compound, ethinyl estradiol. CYCLEN Tablets 28-day are available in a VARIDATE* DIALPAK* Tablet Dispenser containing 28 tablets, 21 of which are blue tablets containing 0.25 mg of the progestational compound norgestimate, together with 0.035 mg of the estrogenic compound ethinyl estradiol, and 7 of which are green tablets containing inert ingredients. Each blue tablet is debossed on each side with "Ortho" and "250", while each green tablet is embossed on each side with the word "Ortho".

TRI-CYCLEN Tablets 21 day are available in a VARIDATE* DIALPAK* Tablet Dispenser containing 21 tablets 7 of which are white, unscored tablets with "Ortho" and "180" debossed on each side; 7 of which are light blue, unscored tablets with "Ortho" and "215" on each side and 7 of which are blue, unscored tablets with "Ortho" and "250" debossed on each side. TRI-CYCLEN Tablets 28 day are available in a VARIDATE* DIALPAK* Tablet Dispenser containing 28 tablets 7 of which are white, unscored tablets with "Ortho" and "180" debossed on each side; 7 of which are light blue, unscored tablets with "Ortho" and "215" on each side and 7 of which are blue, unscored tablets with "Ortho" and "250" debossed on each side and 7 of which are green tablets with "Ortho" debossed on each side. Each white tablet contains 0.180 mg of the progestational compound norgestimate, together with 0.035 mg of the estrogenic compound ethinyl estradiol. Each light blue tablet contains 0.215 mg of the progestational compound norgestimate, together with 0.035 mg of the estrogenic compound ethinyl estradiol. Each blue tablet contains 0.250 mg of the progestational compound norgestimate, together with 0.035 mg of the estrogenic compound ethinyl estradiol. Each green tablet contains inert ingredients.

STORAGE RECOMMENDATIONS Store between 15oC - 25oC. Leave contents in protective package until time of use.

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Detailed directions for use are contained in the Patient Package Insert that is supplied with each package.

ORTHO

PAAB

Supplementary Information Booklets and Product Monographs are available upon request.

Norvasc*

(amlodipine besylate/pfizer)

rief Prescribing Information
ORVASC
mlodipine besylate)
ablets 2.5, 5 and 10 mg
ntihypertensive-Antianginal Agent

CTION AND CLINICAL PHARMACOLOGY
ORVASC (amlodipine besylate) is a calcium ion influx inhibitor (calcium entry blocker or calcium ion antagonist).
mlodipine is a member of the dihydropyridine class of calcium antagonists.

DICATIONS AND CLINICAL USE
ypertension
ORVASC (amlodipine besylate) is indicated in the treatment of mild to moderate essential hypertension.
ORVASC should normally be used in those patients in whom treatment with diuretics or beta-blockers was found effective or has been associated with unacceptable adverse effects. NORVASC can be tried as an initial agent in ose patients in whom the use of diuretics and/or beta-blockers is contraindicated or in patients with medical onditions in which these drugs frequently cause serious adverse effects. Combination of NORVASC with a uretic, a beta-blocking agent, or an angiotensin converting enzyme inhibitor has been found to be compatible and howed additive antihypertensive effect.
hronic Stable Angina
ORVASC is indicated for the management of chronic stable angina (effort-associated angina) in patients who main symptomatic despite adequate doses of beta-blockers and/or organic nitrates or who cannot tolerate those gents. NORVASC may be tried in combination with beta-blockers in chronic stable angina in patients with normal entricular function. When such concomitant therapy is introduced, care must be taken to monitor blood pressure osely since hypotension can occur from the combined effects of the drugs.

ONTRAINDICATIONS
ORVASC (amlodipine besylate) is contraindicated in patients with hypersensitivity to the drug or other hydropyridines and in patients with severe hypotension (less than 90 mmHg systolic).

/ARNINGS
se in Patients with Congestive Heart Failure
afety and efficacy of NORVASC (amlodipine besylate) in patients with heart failure has not been established. aution should therefore, be exercised when using NORVASC in patients with compromised ventricular function, articularly in combination with a beta-blocker. In a controlled clinical trial using a small number of patients 8 Norvasc and 60 Placebo) with well compensated congestive heart failure (NYHA Class II-III), addition of ORVASC to digoxin and diuretic therapy with or without angiotensin converting enzyme inhibitors did not lead to orsening of heart failure in the majority of patients treated.
ıcreased Angina and/or Myocardial Infarction
arely, patients, particularly those with severe obstructive coronary artery disease, have developed ocumented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting alcium channel blocker therapy or at the time of dosage increase. The mechanism of this effect has not een elucidated.
utflow Obstruction (Aortic Stenosis)
ORVASC should be used with caution in a presence of fixed left ventricular outflow obstruction ortic stenosis).
se in Patients with Impaired Hepatic Function
here are no adequate studies in patients with liver dysfunction and dosage recommendations have not been stablished. In a small number of patients with mild to moderate hepatic impairment given single dose of 5 mg, mlodipine half-life has been prolonged. NORVASC should, therefore, be administered with caution in these atients and careful monitoring should be performed. A lower starting dose may be required (see **DOSAGE AND DMINISTRATION**).
eta-blocker Withdrawal
ORVASC gives no protection against the dangers of abrupt beta-blocker withdrawal and such withdrawal should e done by the gradual reduction of the dose of beta-blocker.
RECAUTIONS
ypotension
ORVASC (amlodipine besylate) may occasionally precipitate symptomatic hypotension. Careful monitoring of lood pressure is recommended, especially in patients with a history of cerebrovascular insufficiency, and those king medications known to lower blood pressure.
eripheral Edema
ild to moderate peripheral edema was the most common adverse event in the clinical trials (see **ADVERSE EACTIONS**). The incidence of peripheral edema was dose-dependent and ranged in frequency from 3.0 to 10.8% 5 to 10 mg dose range. Care should be taken to differentiate this peripheral edema from the effects of increasing ft ventricular dysfunction.
se in Pregnancy
though amlodipine was not teratogenic in the rat and rabbit some dihydropyridine compounds have been found be teratogenic in animals. In rats, amlodipine has been shown to prolong both the gestation period and the uration of labor. There is no clinical experience with NORVASC in pregnant women. NORVASC should be used uring pregnancy only if the potential benefit outweighs the potential risk to the mother and fetus.
ursing Mothers
is not known whether amlodipine is excreted in human milk. Since amlodipine safety in newborns has not been stablished, NORVASC should not be given to nursing mothers.
se in Children
he use of NORVASC is not recommended in children since safety and efficacy have not been established in at population.
se in Elderly
elderly patients (≥65 years) clearance of amlodipine is decreased with a resulting increase in AUC. In clinical als the incidence of adverse reactions in elderly patients was approximately 6% higher than that of younger opulation (<65 years). Adverse reactions include edema, muscle cramps and dizziness. NORVASC should be used utiously in elderly patients. Dosage adjustment is advisable (see **DOSAGE AND ADMINISTRATION**).
rug Interactions
eta-blockers: When beta-adrenergic receptor blocking drugs are administered concomitantly with NORVASC, tients should be carefully monitored since blood pressure lowering effect of beta-blockers may be augmented by mlodipine's reduction in peripheral vascular resistance.
goxin, Cimetidine, Warfarin: Pharmacokinetic interaction studies in healthy volunteers have indicated:
mlodipine did not change serum digoxin levels or digoxin renal clearance.
imetidine did not alter the pharmacokinetics of amlodipine.
mlodipine did not change warfarin induced prothrombin response time.

DVERSE REACTIONS
ORVASC (amlodipine besylate) has been administered to 1,714 patients (805 hypertensive and 909 angina itients) in controlled clinical trials (vs placebo alone and with active comparative agents). Most adverse actions reported during therapy were of mild to moderate severity.
/pertension
the 805 hypertensive patients treated with NORVASC in controlled clinical trials, adverse effects were reported 29.9% of patients and required discontinuation of therapy due to side effects in 1.9% of patients. The most mmon adverse reactions in controlled clinical trials were: edema (8.9%), and headache (8.3%).
e following adverse reactions were reported with an incidence of ≥0.5% in the controlled clinical trials ogram (n=805):
rdiovascular: edema (8.9%), palpitations (2.0%), tachycardia (0.7%), postural dizziness (0.5%). **Skin and ppendages:** pruritus (0.7%). **Musculoskeletal:** muscle cramps (0.5%). **Central and Peripheral Nervous System:** headache (8.3%), dizziness (3.0%), paresthesia (0.5%). **Autonomic Nervous System:** flushing (3.1%), increased sweating (0.9%), dry mouth (0.7%). **Psychiatric:** somnolence (1.4%). **Gastrointestinal:** nausea (2.4%), abdominal pain (1.1%), dyspepsia (0.6%), constipation (0.5%). **General:** fatigue (4.1%), pain (0.5%).

Angina
In the controlled clinical trials in 909 angina patients treated with NORVASC, adverse effects were reported in 30.5% of patients and required discontinuation of therapy due to side effects in 0.6% of patients. The most common adverse reactions reported in controlled clinical trials were: edema (9.9%) and headache (7.8%).
The following adverse reactions occurred at an incidence of ≥0.5% in the controlled clinical trials program (n=909):
Cardiovascular: edema (9.9%), palpitations (2.0%), postural dizziness (0.6%). **Skin and Appendages:** rash (1.0%), pruritus (0.8%). **Musculoskeletal:** muscle cramps (1.0%). **Central and Peripheral Nervous System:** headache (7.8%), dizziness (4.5%), paresthesia (1.0%), hypoesthesia (0.9%). **Autonomic Nervous System:** flushing (1.9%). **Psychiatric:** somnolence (1.2%), insomnia (0.9%), nervousness (0.7%). **Gastrointestinal:** nausea (4.2%), abdominal pain (2.2%), dyspepsia (1.4%), diarrhea (1.1%), flatulence (1.0%), constipation (0.9%). **Respiratory System:** dyspnea (1.1%). **Special Senses:** abnormal vision (1.3%), tinnitus (0.6%). **General:** fatigue (4.8%), pain (1.0%), asthenia (1.0%).
NORVASC has been evaluated for safety in about 11,000 patients with hypertension and angina.
The following events occurred in <1% but >0.1% of patients in comparative clinical trials (double-blind comparative vs placebo or active agents; n = 2,615) or under conditions of open trials or marketing experience where a causal relationship is uncertain.
Cardiovascular: arrhythmia (including ventricular tachycardia and atrial fibrilation), bradycardia, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension. **Central and Peripheral Nervous System:** hypoesthesia, tremor, vertigo. **Gastrointestinal:** anorexia, constipation, dysphagia, vomiting, gingival hyperplasia. **General:** asthenia†, back pain, hot flushes, malaise, rigors, weight gain. **Musculoskeletal System:** arthralgia, arthrosis, myalgia. **Psychiatric:** sexual dysfunction (male† and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization. **Respiratory System:** epistaxis. **Skin and Appendages:** pruritus†, rash erythematous, rash maculopapular. **Special Senses:** conjunctivitis, diplopia, eye pain, tinnitus. **Urinary System:** micturition frequency, micturition disorder, nocturia. **Autonomic Nervous System:** dry mouth, sweating increased. **Metabolic and Nutritional:** thirst. **Hemopoietic:** purpura.
†These events occurred in less than 1% in placebo controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.
The following events occurred in ≤0.1% of patients: cardiac failure, skin discoloration, urticaria, skin dryness, alopecia, twitching, ataxia, hypertonia, migraine, apathy, amnesia, gastritis, increased appetite, coughing, rhinitis, parosmia, taste perversion, and xerophthalmia.

SYMPTOMS AND TREATMENT OF OVERDOSAGE
Symptoms
Overdosage can cause excessive peripheral vasodilation with marked and probably prolonged hypotension and possibly a reflex tachycardia. In humans, experience with overdosage of NORVASC (amlodipine besylate) is limited. When amlodipine was ingested at doses of 105-250 mg some patients remained normotensive with or without gastric lavage while another patient experienced hypotension (90/50 mmHg) which normalized following plasma expansion. A patient who took 70 mg of amlodipine with benzodiazepine developed shock which was refractory to treatment and died. In a 19 month old child who ingested 30 mg of amlodipine (about 2 mg/kg) there was no evidence of hypotension but tachycardia (180 bpm) was observed. Ipecac was administered 3.5 hrs after ingestion and on subsequent observation (overnight) no sequelae were noted.
Treatment
Clinically significant hypotension due to overdosage requires active cardiovascular support including frequent monitoring of cardiac and respiratory function, elevation of extremities, and attention to circulating fluid volume and urine output. A vasoconstrictor (such as norepinephrine) may be helpful in restoring vascular tone and blood pressure, provided that there is no contraindication to its use. As NORVASC is highly protein bound, hemodialysis is not likely to be of benefit. Intravenous calcium gluconate may be beneficial in reversing the effects of calcium channel blockade. Clearance of amlodipine is prolonged in elderly patients and in patients with impaired liver function. Since amlodipine absorption is slow, gastric lavage may be worthwhile in some cases.

DOSAGE AND ADMINISTRATION
Dosage should be individualized depending on patient's tolerance and responsiveness. For both hypertension and angina, the recommended initial dose of NORVASC (amlodipine besylate) is 5 mg once daily. If necessary, dose can be increased after 1-2 weeks to a maximum dose of 10 mg once daily.
Use in the Elderly or in Patients with Impaired Renal Function
The recommended initial dose in patients over 65 years of age or patients with impaired renal function is 5 mg once daily. If required, increasing in the dose should be done gradually and with caution (see **PRECAUTIONS**).
Use in Patients with Impaired Hepatic Function
Dosage requirements have not been established in patients with impaired hepatic function. When NORVASC is used in these patients, the dosage should be carefully and gradually adjusted depending on patient's tolerance and response. A lower starting dose of 2.5 mg once daily should be considered (see **WARNINGS**).

DOSAGE FORMS
Availability
NORVASC is available as white octagonal tablets containing amlodipine besylate equivalent to 2.5, 5 and 10 mg amlodipine per tablet. The respective tablet strengths are debossed on one tablet face as "NRV 2.5", "NRV 5" and "NRV 10" with "Pfizer" on the opposite face. The 5 mg tablet is scored. Supplied in white plastic (high density polyethylene) bottles of 100 tablets for each strength. Also the 5 mg and 10 mg are supplied in bottles of 250 tablets.

STORAGE
Store at 15-30°C. Protect from light.

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Kirkland, Quebec
H9J 2M5

PAAB

*TM Pfizer Inc.
Pfizer Canada Inc., licensee

Flovent

(fluticasone propionate inhalation aerosol)
Corticosteroid for Inhalation

ACTIONS AND CLINICAL PHARMACOLOGY

Fluticasone propionate is a highly potent glucocorticoid anti-inflammatory steroid with strong topical and negligible systemic activity. When administered by inhalation at therapeutic dosages, it has a direct potent anti-inflammatory action within the lungs, resulting in reduced symptoms and exacerbations of asthma without the adverse effects observed when corticosteroids are administered systemically. In comparisons with beclomethasone dipropionate, fluticasone propionate has demonstrated greater topical potency.

A portion of an inhaled dose will be swallowed; however, oral bioavailability of fluticasone propionate approaches zero due to poor absorption and extensive first-pass metabolism. Following oral administration, 87-100% of the dose is excreted in the feces, up to 75% as unabsorbed parent compound depending on the dose. Between 1% and 5% of the dose is excreted as metabolites in urine. There is a non-active major metabolite. Following intravenous administration, there is rapid plasma clearance suggestive of extensive hepatic extraction. The plasma elimination half-life is approximately 3 hours. The volume of distribution is approximately 250 litres.

Daily output of adrenocortical hormones remain within the normal range during chronic treatment with inhaled fluticasone propionate, even at the highest recommended doses in children (200 µg/day) and adults (2000 µg/day). After transfer from other inhaled steroids to fluticasone propionate, the daily output gradually improves despite past and present intermittent use of oral steroids, thus demonstrating return of normal adrenal function on inhaled fluticasone propionate. The adrenal reserve also remains normal during chronic treatment with inhaled fluticasone propionate, as measured by a normal increment on a stimulation test. However, any residual impairment of adrenal reserve from previous treatments may persist for a considerable time.

INDICATIONS AND CLINICAL USE

Flovent is indicated for the prophylactic management of steroid-responsive bronchial asthma in adults and children over 4 years of age.

Adults and adolescents above 16 years of age

Flovent can be used for: Mild asthma – PEF values greater than 80% of predicted at baseline with less than 20% variability. Patients requiring intermittent symptomatic bronchodilator asthma medication on more than an occasional basis. Moderate asthma – PEF values 60-80% of predicted at baseline with 20-30% variability. Patients requiring regular asthma medication and patients with unstable or worsening asthma on currently available prophylactic therapy or bronchodilator alone. Severe asthma – PEF values less than 60% of predicted at baseline with greater than 30% variability. Patients with severe, chronic asthma. On introduction of *Flovent*, many patients who are dependent on systemic corticosteroids for adequate control of symptoms may be able to reduce significantly or to eliminate their requirements for oral corticosteroids. Severe asthma requires regular medical assessment as death may occur. Patients with severe asthma have constant symptoms and frequent exacerbations, with limited physical capacity. These patients will require high dose inhaled or oral corticosteroid therapy. Sudden worsening of symptoms may require increased corticosteroid dosage which should be administered under urgent medical supervision.

Children above 4 years of age

Flovent is indicated for any child > 4 years of age who requires prophylactic medication, including patients not controlled on currently available therapy.

CONTRAINDICATIONS

Flovent is contraindicated in patients with a history of hypersensitivity to any of its ingredients and in patients with active or quiescent pulmonary tuberculosis, or untreated fungal, bacterial or viral infections of the respiratory tract. It is not to be used in the primary treatment of status asthmaticus or other acute episodes of asthma, or in patients with moderate to severe bronchiectasis.

WARNINGS AND PRECAUTIONS

General: Patients must be instructed that *Flovent* is a preventative agent to be taken daily at the intervals recommended by their doctors and is not to be used as acute treatment for an asthmatic attack. Patients should be advised to inform subsequent physicians of the prior use of corticosteroids.

Systemic Steroid Replacement by Inhaled Steroid: Particular care is needed in asthmatic patients who are transferred from systemically active to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred during and after transfer. In addition, systemic symptoms (e.g. joint and/or muscular pain, lassitude, depression) may occur upon withdrawal despite maintenance or improvement of respiratory function. Recovery from impaired adrenocortical function, caused by prolonged systemic therapy, is slow. The transfer of patients being treated with oral corticosteroids must be gradual and carefully supervised by the physician; the guidelines under DOSAGE AND ADMINISTRATION should be followed.

Patients with adrenocortical suppression should be monitored regularly and the oral steroid reduced cautiously. Adrenal function and adrenal reserve usually remain within the normal range on *Flovent*; however, some systemic effects may occur in a small proportion of adult patients after prolonged treatment at the maximum recommended daily dose. Patients transferred from other inhaled steroids or oral steroids remain at risk of impaired adrenal reserve for a considerable time after transferring to *Flovent*. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA) function. During this period of HPA suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery or infections, particularly gastroenteritis. Although *Flovent* may provide control of asthmatic symptoms during these episodes, it does not provide the systemic steroid which is necessary for coping with these emergencies. The physician may consider supplying oral steroids for use in times of stress (e.g. worsening asthma attacks, chest infections, surgery).

During periods of stress or a severe asthmatic attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume systemic steroids immediately and to contact their physician for further instruction. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic steroids during these periods. To assess the risk of adrenal insufficiency in emergency situations, routine tests of adrenal cortical function, including measurement of early morning and evening cortisol levels, should be performed periodically in all patients. An early morning resting cortisol level may be accepted as normal only if it falls at or near the normal mean level.

Transfer of patients from systemic steroid therapy to *Flovent* may unmask allergic conditions outside the pulmonary tract that were previously suppressed by the systemic steroid therapy, (e.g., rhinitis, conjunctivitis, and eczema.) These allergies should be symptomatically treated with antihistamine and/or topical preparations, including topical steroids.

Candidiasis and oral hygiene: Therapeutic dosages frequently cause hoarseness or the appearance of Candida albicans (thrush) in the mouth and throat. Adequate oral hygiene is of primary importance in minimizing overgrowth of micro-organisms such as Candida albicans. The development of pharyngeal and laryngeal candidiasis is a cause for concern because the extent of its penetration into the respiratory tract is unknown. Patients may find it helpful to rinse out their mouths with water after using the inhaler. Cleansing dentures has the same effect. Symptomatic candidiasis can be treated with topical anti-fungal therapy while still continuing to use *Flovent*.

Paradoxical Bronchospasm: As with other inhalation therapy, paradoxical bronchospasm may occur characterized by an immediate increase in wheezing after dosing. This should be treated immediately with a fast-acting inhaled bronchodilator (e.g. salbutamol) to relieve acute asthmatic symptoms. *Flovent* should be discontinued immediately, the patient assessed, and if necessary, alternative therapy instituted.

Monitoring Asthma Control: Increasing use of short-acting inhaled bronchodilators to control symptoms indicates deterioration of asthma control. Sudden and progressive deterioration in asthma control is potentially life-threatening and consideration should be given to increasing corticosteroid dosage. Patients should be instructed to contact their physicians if they find that relief with short-acting bronchodilator treatment becomes less effective or they need more inhalations than usual. During such episodes, patients may require therapy with systemic corticosteroids.

Flovent is not indicated for rapid relief of bronchospasm but for regular daily treatment of the underlying inflammation. There is no evidence that control of bronchial asthma can be achieved by the administration of *Flovent* in amounts greater than the recommended dosages.

Lack of response or severe exacerbations of asthma should be treated by increasing the dose of *Flovent* and, if necessary, by giving a systemic steroid and/or an antibiotic if there is an infection.

Long Term Effects: The long-term effects of fluticasone propionate in human subjects are still unknown. In particular, the local effects of the drug on developmental or immunologic processes in the mouth, pharynx, trachea, and lungs are unknown. There is also no information about the possible long-term systemic effects of the agent. During long-term therapy, HPA axis function and haematological status should be assessed periodically.

Discontinuance: Treatment with *Flovent* should not be stopped abruptly, but tapered off gradually.

Pulmonary Infiltration by Eosinophils: As with other glucocorticoids, pulmonary infiltration by eosinophils may occur in patients on *Flovent* therapy. Although it is possible that in some patients this state may become manifest because of systemic steroid withdrawal when inhaled steroids are administered, a causative role for fluticasone propionate and/or its vehicle cannot be ruled out.

Pregnancy: The safety of fluticasone propionate in pregnancy has not been established. The expected benefits should be weighed against the potential risk to the fetus, particularly during the first trimester of pregnancy. Like other glucocorticoids, fluticasone propionate is teratogenic to rodent species. Adverse effects typical of potent corticosteroids are only seen at high systemic exposure levels; administration by inhalation ensures minimal systemic exposure. The relevance of these findings to humans has not yet been established since well-controlled trials relating to foetal risk in humans are not available. Infants born of mothers who have received substantial doses of glucocorticoids during pregnancy should be carefully observed for hypoadrenalism.

Lactation: Glucocorticoids are excreted in human milk. The excretion of fluticasone propionate into human breast milk has not been investigated. When measurable plasma levels were obtained in lactating laboratory rats following subcutaneous administration there was evidence of fluticasone propionate in the breast milk. However, plasma levels in patients following inhaled fluticasone propionate at recommended doses are likely to be low. The use of fluticasone propionate in nursing mothers requires that the possible benefits of the drug be weighed against the potential risk to the infant.

Children: *Flovent* is not presently recommended for children younger than 4 years of age due to limited clinical data in this age group.

Effect on Infection: Corticosteroids may mask signs of infections and new infections may appear. Decreased resistance to localised infection has been observed during corticosteroid therapy. This may require treatment with appropriate therapy or stopping *Flovent* therapy until the infection is eradicated.

Abuse of Fluorocarbon Propellants: Fluorocarbon propellants may be hazardous if they are deliberately abused. Inhalation of high concentrations of aerosol sprays has brought about cardiovascular toxic effects and even death, especially under conditions of hypoxia. However, evidence attests to the safety of aerosols when used properly with adequate ventilation.

Hypothyroidism and Cirrhosis: There is an enhanced effect of corticosteroids on patients with hypothyroidism and in those with cirrhosis.

Use of Corticosteroids and Acetylsalicylic Acid (ASA): ASA should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia.

Proper Use of the Inhaler: To ensure the proper dosage and administration of the drug, the patient must be instructed by a physician or other health professional in the use of the inhaler. Inhaler actuation should be synchronised with inspiration to ensure optimum delivery of the drug to the lungs.

Drug interaction: No specific drug interaction studies have been performed; however, because of the very low plasma drug concentrations achieved after inhaled dosing, there are unlikely to be any implications for displacement drug interactions. There were no reports of suspected drug interactions in clinical trials with *Flovent*.

ADVERSE REACTIONS

No major side effects attributable to the use of *Flovent* have been reported. Adverse reactions in controlled clinical studies with *Flovent* have been primarily those normally associated with asthma. Apart from asthma and related events and pharmacologically predicted events (e.g. candidiasis and hoarseness), there were no dose-related trends. Cutaneous hypersensitivity reactions have been observed. The adverse reactions reported by patients treated with *Flovent* were similar to those reported by patients treated with beclomethasone dipropionate. The most frequently reported adverse reactions (≥1%) considered by the investigator to be potentially drug-related during controlled clinical trials in over 4400 adults and 1100 children are presented below.

	Percentage of Patients Reporting Adverse Reactions	
	Adults (≥16 years) (n = 3640)	Children (4-16 years) (n = 778)
Asthma & related events	2	3
Oral candidiasis	3	<1
Hoarseness	2	<1
Sore throat	1	<1
Cough	1	1

Infrequent adverse reactions (0.1-1%) reported by patients receiving recommended dosages of *Flovent* (200-2000 µg/day for adults; 100-200 µg /day for children) in these clinical trials included headache, musculoskeletal pain, diabetes, hypertension, weight gain, viral infection, respiratory tract infection, nausea, gastric pain, allergy, depression, and oral ulcer.

Adrenal Suppression: No indication of significant adrenal cortical suppression has been observed when the daily dosage was up to 2 mg. Above this dosage, reduction of plasma cortisol may occur.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

The acute toxicity of fluticasone propionate is low. The only harmful effect that follows inhalation of large amounts of the drug over a short period of time is suppression of adrenal function. No special emergency action need be taken. In such cases, treatment with *Flovent* should be continued at a dose sufficient to control asthma; adrenal function recovers in a few days and can be verified by measuring plasma cortisol. Chronic use of *Flovent* in daily doses in excess of 2 mg may lead to some degree of adrenal suppression. Monitoring of adrenal reserve may be indicated. Gradual dose reduction may be required. Treatment with *Flovent* should be continued at a dose sufficient to control asthma.

DOSAGE AND ADMINISTRATION

General: *Flovent* is to be administered by the inhaled route only. Since the effect of *Flovent* depends on its regular use and on the proper technique of inhalation, the patient should be made aware of the prophylactic nature of therapy and that for optimum benefit *Flovent* should be taken regularly, even when the patient is asymptomatic.

Patients using inhaled bronchodilators should be advised to use the bronchodilator before *Flovent* in order to enhance the penetration of *Flovent* into the bronchial tree. Several minutes should lapse between the use of the two inhalers to reduce the potential toxicity from the inhaled fluorocarbon propellants and to allow for some bronchodilation to occur. If patients find that relief with short-acting bronchodilator treatment becomes less effective or they need more inhalations than usual, medical attention should be sought.

In the presence of excessive mucous secretion, the drug may fail to reach the bronchioles. Therefore, if an obvious response is not obtained after ten days, attempts should be made to remove the mucous with expectorants and/or with a short course of systemic corticosteroids. Continued *Flovent* treatment usually maintains the improvement, systemic steroid is gradually withdrawn. As a general rule, rinsing the mouth and gargling after each inhalation with water can help in preventing the occurence of candidiasis. Cleansing dentures has the same effect.

Treatment with *Flovent* should not be stopped abruptly, but tapered off gradually.

Administration: Patients must be instructed in the correct method of using the *Flovent* Inhaler to ensure that the drug reaches the target areas within the lungs. Each prescribed dose should be given by a minimum of 2 inhalations. Before the first use, and after a long period without use, the inhaler should be primed before treatment by actuating the inhaler 4 times. Inhaler actuation should be synchronised with inspiration to ensure optimum delivery of drug. In patients who find co-ordination of a pressurised metered dose inhaler difficult, a spacer device such as VENT-A-HALER® may be used.

Dosage: The dosage should be adjusted according to individual response.

Adults and adolescents above 16 years of age – Usual dosage of *Flovent* is 100 to 500 µg twice daily. Patients should be given a starting dose which is appropriate for the severity of their disease as follows:

Mild asthma	100 to 250 µg twice daily
Moderate asthma	250 to 500 µg twice daily.
Severe asthma	500 µg twice daily. Very severe patients requiring higher doses of corticosteroids such as those patients currently requiring oral steroids may use doses up to 1000 µg twice daily.

The dose may then be adjusted until control is achieved or reduced to the minimum effective dose according to the individual response. Alternatively, the starting dose of *Flovent* may be gauged at half the total daily dose of beclomethasone dipropionate or equivalent as administered by metered-dose inhaler. Onset of effect occurs within 4-7 days of the start of treatment with *Flovent*. If no improvement is noted in this time frame, an increase in dose should be considered.

Children (over 4 years of age) – Children should be given a starting dose of *Flovent*, either 50 or 100 µg twice daily, which is appropriate for the severity of their disease. The dose may then be adjusted until control is achieved or reduced to the minimum effective dose according to the individual response.

Special patient groups – There is no need to adjust the dose in elderly patients or those with hepatic or renal impairment.

Patients receiving systemic steroids – The transfer of steroid-dependent patients to *Flovent* and their subsequent management needs special care. Patients' bronchial asthma should be stable before being given *Flovent* in addition to the usual maintenance dose of systemic steroid. After about a week, gradual withdrawal of the systemic steroid is started by reducing the daily dose by 1.0 mg of prednisone (or its equivalent) at not less than weekly intervals, under close observation. In children, the usual rate of withdrawal is 1.0 mg of the daily dose of prednisone every eight days, under close supervision. If continuous supervision is not feasible, the withdrawal of the systemic steroid should be slower, approximately 1.0 mg of the daily dose of prednisone (or equivalent) every ten and every twenty days in adults and in children, respectively. A slow rate of withdrawal cannot be over-emphasized.

If withdrawal symptoms appear, the previous dose of the systemic drug should be resumed for a week before any further decrease is attempted. Patients who have been treated with systemic steroids for long periods of time or at a high dose may have adrenocortical suppression. In these patients adrenocortical function should be monitored regularly and their dose of systemic steroid reduced cautiously. Some patients feel unwell during the withdrawal phase experiencing symptoms such as joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function. Such patients should be encouraged to persevere with *Flovent* but should be watched carefully for objective signs of adrenal insufficiency such as hypotension and weight loss. If evidence of adrenal insufficiency occurs, the systemic steroid dosage should be boosted temporarily and thereafter further withdrawal should be continued more slowly.

Transferred patients whose adrenocortical function is impaired should carry a warning card indicating that they need supplementary treatment with systemic steroids during periods of stress, (e.g. surgery, chest infection, or severe asthma attack.) Consideration should be given to supplying such patients with oral steroids to use in an emergency. The dose of *Flovent* should be increased at this time and then reduced to the maintenance level after the systemic steroid has been discontinued.

Exacerbations of bronchial asthma which occur during the course of treatment with *Flovent* should be treated with a short course of systemic steroid which is gradually tapered as these symptoms subside. Under stressful conditions or when the patient has a severe exacerbation of bronchial asthma, after complete withdrawal of the systemic steroid, use of the latter must be resumed in order to avoid relative adreno-cortical insufficiency.

Some patients cannot completely discontinue oral corticosteroid. In these cases, a minimum maintenance dose should be given in addition to *Flovent*.

PHARMACEUTICAL INFORMATION

Composition: *Flovent* Inhaler is an aerosol, delivering 25, 50, 125, or 250 µg of fluticasone propionate (micronised) per puff, suspended in trichlorofluoromethane and dichlorodifluoromethane. Also contains lecithin.

Stability and Storage Recommendations: Store between 2° and 30° C. Protect from frost and direct sunlight. Contents under pressure. Container may explode if heated. Do not place in hot water or near radiators, stoves, or other sources of heat. Even when apparently empty, do not puncture or incinerate container or store at temperatures over 30° As with most inhaled medications in pressurised canisters, the therapeutic effect of this medication may decrease when the canister is cold.

Availability: *Flovent* Inhalers are metered-dose aerosols of fluticasone propionate in an aluminum canister fitted with a metering valve. Each unit is housed in a suitable actuator/adaptor. *Flovent* Inhalers are available in four strengths: 25 µg/actuation, 50 µg/actuation, 125 µg/actuation, or 250 µg/actuation. Each strength is available in 60 dose and 120 dose containers.

Full prescribing information available to physicians and pharmacists upon request. Please contact Glaxo Wellcome Inc., 7333 Mississauga Rd. North, Mississauga, Ontario L5N 6L4 or call 1-800-268-0324.

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Flovent®

(fluticasone propionate inhaler)

Less than 1% oral systemic availability Glaxo Wellcome Inc.

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LOZIDE

(Indapamide)

In a class of its own

The only indoline diuretic

LOZIDE
(indapamide)
1.25 and 2.5 mg Tablets
Diuretic/Antihypertensive Agent

INDICATION AND CLINICAL USE
LOZIDE is indicated in the management of essential hypertension. It may be tried as a sole therapeutic agent in the treatment of mild to moderate hypertension. Normally LOZIDE, as other diuretics, is used as the initial agent in multiple drug regimens.

CONTRAINDICATIONS
Anuria, progressive and severe oliguria, hepatic coma. Known sensitivity to indapamide or to other sulfonamide derivatives.

WARNINGS
Electrolyte changes observed with indapamide become severe at doses above 2.5 mg per day. Therefore, the maximum daily dose should not exceed this dose.

Hypokalemia may occur at all doses with consequent weakness, cramps and cardiac dysrhythmias. Hypokalemia is a particular hazard in digitalized patients; dangerous or fatal cardiac arrhythmias may be precipitated.

Hypokalemia occurs commonly with diuretics; electrolyte monitoring is essential particularly in patients who would be at increased risk from hypokalemia, such as patients with cardiac arrhythmias or those who are receiving concomitant cardiac glycosides.

Patients with renal insufficiency receiving indapamide should be carefully monitored. If increasing azotemia and oliguria occur during treatment, the diuretic should be discontinued.

Hyperuricemia may occur during administration of indapamide. Rarely gout has been reported. Blood uric acid levels should be monitored, particularly in patients with a history of gout who should continue to receive appropriate treatment.

PRECAUTIONS
Patients receiving indapamide should be carefully observed and serum electrolytes monitored for signs and symptoms of fluid or electrolyte imbalance; namely hyponatremia, hypochloremia and hypokalemia. Blood urea nitrogen, uric acid, and glucose levels should also be assessed during therapy. Hypokalemia, an ever present hazard with most diuretics, will be more common in association with concomitant steroid or ACTH therapy and with inadequate electrolyte intake. The serum potassium should be determined at regular intervals and potassium supplementation instituted when indicated. (See WARNINGS)

The signs of electrolyte imbalance are: dryness of the mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscle fatigue, hypotension, oliguria, gastrointestinal disturbances such as nausea and vomiting, tachycardia and ECG changes.

Special caution should be used in treating patients with severe hepatic disease since diuretics may induce metabolic alkalosis in cases of potassium depletion which may precipitate episodes of hepatic encephalopathy.

Orthostatic hypotension may occur and may be potentiated by alcohol, barbiturates, narcotics or concurrent therapy with other antihypertensives.

When indapamide is given with other non-diuretic antihypertensive agents, the effects on blood pressure are additive.

Sulfonamide derivatives have been reported to exacerbate or activate systemic lupus erythematosus. These possibilities should be kept in mind with the use of indapamide although no case has been reported to date.

Severe dermatological adverse reactions, some accompanied by systemic manifestations, have been rarely reported with the use of indapamide. In the majority of cases, the condition subsided within 14 days following discontinuation of indapamide therapy. (See ADVERSE REACTIONS)

Caution should be observed when administrating the drug to patients with severely impaired renal function, since the drug is excreted primarily by the renal route.

Although indapamide exerts minimal effect on glucose metabolism, insulin requirements may be affected in diabetics and hyperglycemia and glycosuria may occur in patients with latent diabetes.

Calcium excretion is decreased by diuretics pharmacologically related to indapamide. After six to eight weeks of indapamide 1.25 mg treatment and in long-term studies of hypertensive patients with higher doses of indapamide, however, serum concentrations of calcium increased only slightly with indapamide. Prolonged treatment with drugs pharmacologically related to indapamide may in rare instances be associated with hypercalcemia and hypophosphatemia secondary to physiologic changes in the parathyroid gland; however, the common complications of hyperparathyroidism, such as renal lithiasis, bone resorption, and peptic ulcer, have not been seen. Treatment should be discontinued before tests for parathyroid function are performed. Like the thiazides, indapamide may decrease serum PBI levels without signs of thyroid disturbance.

The antihypertensive effect of the drug may be enhanced in the patient postsympathectomy.

Use in Pregnancy
Since indapamide has not been studied in human pregnancy, the drug should not be given to pregnant women. The use in patients of childbearing potential requires that the anticipated benefit be weighed against possible hazards.

Use in Nursing Mothers
It is unknown whether or not indapamide appears in breast milk. Indapamide should not be administered to nursing mothers. If use of the drug is deemed essential, the patient should stop nursing.

Use in Children
The safety and effectiveness have not been established.

ADVERSE REACTIONS
The safety data presented under this section involves two different databases and was obtained at two different time periods. For the earliest database (indapamide 2.5 mg), consisting mainly of European studies performed before 1980, adverses events were collected with respect to a possible causal relationship to treatment, whereas for the most recent database (indapamide 1.25 mg), consisting exclusively of North-American studies, adverse events were collected irrespective of such a causal relationship. This explains why the overall incidence of adverse events at the 2.5 mg dose appears to be lower than at the 1.25 mg dose (see below).

Most adverse events for both dosages, 1.25 mg and 2.5 mg, have been mild or moderate.

The adverse reactions represent data from clinical studies involving a total of 992 patients given indapamide 2.5 mg: 349 patients from 4 placebo controlled studies treated for 8 to 12 weeks; 356 patients from 6 active controlled studies treated for 6 up to more than 52 weeks; 287 patients from 4 uncontrolled studies treated for 6 up to 40 weeks.

The overall rate of adverse events, with respect to a possible causal relationship to the drug, was 29% and discontinuation of therapy due to adverse events was required in 5.6% of patients.

The most severe and common adverse event is the electrolyte imbalance. Electrolyte changes reported include hypokalemia (14.2%; requiring potassium supplementation 6%; with clinical symptoms 1.2%), hypochloremia (9.4%) and hyponatremia (3.1%).

The other changes observed in laboratory parameters are minor and infrequent: elevation in blood uric acid (8.6%), blood glucose (6.0%), BUN (5.7%) and blood creatinine (3.6%).

The most frequent adverse events (incidence ≥ 1%) reported for patients treated with indapamide 2.5 mg were: headache (3.4%), vertigo (2.2%), dizziness (1.9%), asthenia (1.7%) and muscle cramps (1.2%).

All other adverse events occured at an incidence of less than 1% and included by body system:

Central Nervous: drowsiness, sleepiness, insomnia, weakness, lethargy and visual disturbance.

Gastrointestinal: nausea, anorexia, dryness of mouth, gastralgia, vomiting, diarrhea and constipation.

Musculoskeletal: joint pain, back pain and weakness of legs.

Cardiovascular: orthostatic hypotension, tachycardia and ECG changes (non specific ST-T change, U waves, left ventricular strain).

Urogenital: impotence, modification of libido and polyuria.

Dermatological: rash and pruritus.

Endocrine: gout.

Other: tinnitus, malaise, fainting and sweat.

In placebo-controlled studies involving 306 patients given indapamide 1.25 mg and 319 given placebo for up to eight weeks, the overall incidence of adverse events, irrespective of causal relationship, was about 50% in both indapamide and placebo groups. In the indapamide 1.25 mg group, 4.2% of patients discontinued treatment because of adverse events.

In these studies, 20% of patients treated with indapamide 1.25 mg had at least one potassium value below 3.4 mEq/L.

The most frequently reported adverse events (incidence ≥ 1%) in the indapamide 1.25 mg group were: headache (17%), infection (12%), pain (8%), dizziness (7%), back pain (5%), rhinitis (5%), asthenia (4%), dyspepsia (4%), flu syndrome (3%), hypertonia (3%), sinusitis (3%), chest pain (2%), constipation (2%), cough (2%), diarrhea (2%), edema (2%), nausea (2%), pharyngitis (2%), conjunctivitis (1%), nervousness (1%) and ECG abnormalities [non-specific ST-T changes (7%), sinus bradycardia (3%), arrhythmia (2%) or tachycardia (2%)].

All other clinical adverse events occured at an incidence of less than 1%. These are the following:

Central Nervous: agitation, amnesia, anxiety, ataxia, coordination abnormality, depression, dream abnormality, hyperesthesia, insomnia, migraine, paresthesia, somnolence, twitching and vertigo.

Gastrointestinal: increased appetite, dry mouth, GI carcinoma, GI disorders, duodenitis, dysphagia, esophagitis, flatulence, gastritis, gastroenteritis, oral moniliasis, proctitis, rectal disorders, rectal hemorroïds, stomatitis, tooth disorders and vomiting.

Musculoskeletal: arthralgia, arthritis, bone disorders, joint disorders, bone fracture, bone pain, chondrodystrophy, myalgia, myasthenia and myopathy.

Cardiovascular: angina pectoris, bundle branch block, ventricular extrasystoles, atrial fibrillation, atrial flutter, hypertension, postural hypotension, palpitations, syncope, supraventricular tachycardia and vasodilation.

Urogenital: dysmenorrhea, dysuria, impotence, urinary tract infection, nocturia, oliguria, urinary frequency or urgency, renal pain or calculus, prostate disorders and vaginitis.

Respiratory: bronchitis, dyspnea, laryngitis, lung disorder and sputum increase.

Dermatological: acne, application site reaction, exfoliative dermatitis, nail disorder, skin nodule, rash, bullous eruption and sweat.

Metabolic and nutritional: diabetes mellitus and gout.

Special senses: amblyopia, ear disorders, ear pain, otitis, photophobia, taste perversion, tinnitus and vision abnormality.

Other: thyroid disorder, ecchymosis, allergic reaction, edema face, fever, hernia, malaise and monilia.

Postmarketing experience
Among the less common suspected adverse reactions reported, the following, which are not included elsewhere in the Product Monograph, have been published in the medical literature and/or are classified as serious or potentially serious: Stevens-Johnson syndrome, bullous eruption, photosensitivity with bullae, erythroderma, purpura, epidermal necrolysis, erythema multiforme, angioedema, cataract, acute myopia, optic neuritis, ventricular arrhythmia, torsades de pointe, stroke, acute hypersensitivity reaction leading to interstitial nephritis and renal failure, anemia, agranulocytosis, metabolic alcalosis, hyperosmolar coma, dehydratation, hepatitis, pancreatitis, lithium toxicity, rhabdomyolysis, vasculitis, fever.

One case of synergetic effect of clofibrate with indapamide leading to hyponatremia, hypokalemia, hypoosmolarity, nausea and progressive loss of consciousness.

Relationship with the administration of indapamide has not been proved in all cases.

DOSAGE AND ADMINISTRATION
One 1.25 mg tablet per day taken in the morning as a single dose. If the response is not satisfactory after 4 to 8 weeks, the dose may be increased to a maximum of 2.5 mg as a single dose taken in the morning. If the antihypertensive response to LOZIDE is insufficient, an increase in dosage is not recommended (see WARNINGS).

Instead, a non-diuretic antihypertensive agent should be added to the drug regimen. Alternatively if in the opinion of the physician, an important diuretic effect is desirable for the patient's control, a different diuretic which allows for dose titration could be tried instead of indapamide.

AVAILABILITY OF DOSAGE FORMS
LOZIDE tablets 1.25 mg are available in blisterpacks containing 30 or 100 tablets. Each round, orange, film-coated tablet contains indapamide hemihydrate 1.25 mg; 'S' embossed on one side.

LOZIDE tablets 2.5 mg are available in blisterpacks containing 30 or 100 tablets. Each pink, sugar-coated tablet contains indapamide hemihydrate 2.5 mg.

Product Monograph available upon request

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DEADLINE DATES

Issue	Closing Date (12 noon)
Apr 1	Mar 1
Apr 15	Mar 15

Classifications

C- 1 Conferences
C- 2 Continuing Education
C- 3 Fellowships
C- 4 Locum Tenens Available
C- 5 Locum Tenens Wanted
C- 6 Medical Equipment
C- 7 Miscellaneous
C- 8 Office Space for Rent
C- 9 Placement Agencies
C-10 Positions Vacant
C-11 Positions Wanted
C-12 Practices for Sale
C-13 Practices Wanted
C-14 Real Estate
C-15 Residencies
C-16 Vacations

PLACEMENT OF ADS BY TELEPHONE NOT ACCEPTED

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1/3 page –	1455	1/8 page –	960

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DATES LIMITES DE RÉCEPTION

Numéro	Date limite (à midi)
1er avr	1er mars
15 avr	15 mars

Catégories

C- 1 Conférences
C- 2 Éducation permanente
C- 3 Bourses et stages
C- 4 Remplaçants disponibles
C- 5 Remplaçants demandés
C- 6 Matériel à usage médical
C- 7 Divers
C- 8 Bureaux et locaux à louer
C- 9 Agences de placement
C-10 Postes vacants
C-11 Demandes de postes
C-12 Cabinets à vendre
C-13 Cabinets demandés
C-14 Immobilier
C-15 Résidences
C-16 Vacances

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Ottawa (ON) K1G 0G8

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En annonçant dans le JAMC*, vous êtes assurés d'être publié à près de 60 000 exemplaires deux fois par mois.*

Conferences

AUG. 25 - SEPT. 1, 1996

ALASKA CRUISE

M.S. RYNDAM - Holland America Lines

Updates: osteoporosis asthma
depression diabetes

FAMILY MEDICINE into the 21st CENTURY

Discuss health care reform
with president of B.C.'s society of GPs

save up to $3600/couple (before Feb. 23)

Contact: Pam, tel (604) 589-6111
fax (604) 589-8955 Sonia (800) 661-5611
1710

Locum Tenens Available

EXPERIENCED RADIOLOGIST: Available from mid-February for both short and/or long-term locums. If interested please contact: Box 724, CMAJ. –1804

Locum Tenens Wanted

EMERGENCY LOCUM: ON – Excellent opportunity available for an FRCP, FACEP or CCFP(EM) physician to provide coverage for the months of July and August 1996. Our group of 12 full-time emergency physicians provide coverage in a free-standing, 16-hour, suburban urgent care centre as well as a tertiary care teaching hospital emergency department. Excellent case mix, fair shift distribution and attractive fee-for-service remuneration. Annual volume of 80 000 visits. Contact: Dr. A. Bellissimo, Emergency Department, St. Joseph's Hospital, 50 Charlton Ave. E, Hamilton, ON L8N 4A6; fax (905) 521-6062. –1823

EMERGENCY PHYSICIANS: ON – Emergency physician positions are available for the months of July and August 1996 in Bracebridge. These physicians provide coverage for the emergency department of an 84-bed hospital for the summer months. ACLS and ATLS mandatory. A good work schedule with generous time off, excellent remuneration and a multispecialty backup are some of the advantages to these positions. Beautiful vacationland area with full recreational amenities. Reply to: Darlene Fraser, Administration office, South Muskoka Memorial Hospital, 75 Ann St., Bracebridge, ON P1L 2E4. –1679

GENERAL PRACTICE CLINIC: BC – Prince Rupert. Available locum dates: June 8 to Aug. 17 1996, flexible. 60/40 split, one-in-nine call rotation. Preferably with obstetrics. Full specialist backup and northern living allowance. Accommodation and car provided. Contact Dr. E. Cunningham, tel (604) 624-3331. –1828

LONG-TERM LOCUM / ASSOCIATE: BC – Required immediately for busy, thriving family practice in northeastern British Columbia. Rural town, population approximately 5500. Offers an excellent recreation centre, excellent educational facilities, numerous outdoor recreational activities i.e. canoeing, hunting, fishing, biking, hiking. This is a small town centre 1 hour away from Powder King Ski Resort. Also 1 hour from specialist centre. Expected gross earning in excess of $150 000 per year. Obstetrics and emergency work required but not essential. Start immediately with a one-in-four call. Reply to: Box 704, CMAJ. –1543

SALARIED LOCUM: BC – New Aiyansh, Nass Valley, BC for First Nation (Nisga'a) Community Health Centre. Exquisite location in modern facilities. Good specialist backup nearby. No obstetrics. Shared on-call with physician and nurses required. Northern and isolation allowance, housing and relocation expenses provided. For further information, please phone (604) 633-2212 or fax (604) 633-2512 to the attention of Mr. Reginald Percival, Executive Director, or Dr. Isaac Sobol. –9007

PHYSICIAN: BC – Long-term locum required to do evening shifts in busy Vancouver clinic; 100% of billings. Contact: Dr. G. Baldwin, tel (604) 299-9769. –9988

MATERNITY LOCUM: ON – Ottawa. Family physician needed for part-time family practice. Five 1/2 days per week. May 1996 to January 1997. Call (613) 225-1280 or (613) 798-1174. –1835

FAMILY PHYSICIAN: ON – Locum required May 13 - August 11. Beautiful well-equipped practice with excellent staff in St. Catharines; one-in-six call. Optional urgent care clinic and obstetrics work. Option of associateship and extension. Contact: Dr. Shari Fallis, tel (905) 684-3314, fax (905) 684-2217. –1801

FAMILY PRACTICE: ON – East coast Vancouver Island family practice (group of six) seeks summer (1996) locum with possibility of long-term locum (18 months). Possibility of joining practice. One-in-eight on call. No obstetrics. Twenty minutes to Nanaimo and Duncan. Call Dr. J. Lisinski as soon as possible, (604) 245-2235. –1779

FAMILY PHYSICIAN: ON – Short-term or long-term locum with option of associateship or purchase of clinic, to join family physician in rural family practice. Fee for service. Growing village of 1000 on Highway 38, 35 km from Queen's University, Kingston, and its teaching hospitals. Also draw from several similar communities in area. Beautiful lake country. Recently expanded, spacious modern office with all necessary services. On-call 1 weekend in 5. Approved underserviced area program. Excellent CME and recreational facilities. Combines best of rural living with closeness of university centre. Contact: Dr. H.G. Day, PO Box 10, Verona, ON K0H 2W0; or tel (613) 374-2077. –9959

FAMILY PRACTICE PHYSICIANS: PE – Family practice locum physicians are being sought for several placements in the province of Prince Edward Island: family practice, Crapaud (weeks of Mar. 17-31, 1996); family practice, Souris (week of Mar. 18-24, 1996); emergency room, Charlottetown (period of 2-4 months); family practice locums for summer months (July, August and September). Compensation for physician services is on a fee-for-service basis and an allowance is provided for accommodation. For further information, please contact Gail Millar at the Medical Society of PEI, 559 North River Rd., Charlottetown, PE C1E 1J7; tel (902) 368-1572, fax (902) 566-3934. –1843

AUSTRALIA: – FRCPS or board-certified physicians (generalists and specialists) needed for 6–24-month assignments in Australia. Travel, housing and malpractice insurance all provided along with competitive income. Some positions require ability to function independently in rural settings. For additional information, fax CV to: Global Medical Staffing, Salt Lake City office, (801) 561-9864; or tel (801) 561-9890; (800) 760-3174 (from within Canada). –9937

Miscellaneous

CANADIAN STAMP COLLECTORS: – I have a good selection of pre-war plate blocks and scarce issues. Write: Dr. Dr. R.N. Wright, 62 Leggett Ave., Weston, ON M9P 1X4 stating desires and I will send/or "have a look" by registered mail. No phone. –1722

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–9913

TUTOR WANTED: ON – To assist Canadian graduate to pass LMCC (Medical Council exam). Please reply, stating qualifications, to: Box 726, CMAJ. –1807

Office Space

MEDICAL OFFICE SPACE, ST. CATHARINES: ON – Available immediately, north-end location. Well-maintained, established medical centre including family physicians, cardiologist, laboratory, x-ray/ultrasound, pharmacy, physiotherapy, dentists, optometrist. Wheelchair access, elevator, ample parking. Community hospitals less than 10 minutes away. Attractive leasing options available. Please call Alice Sirard, (416) 935-1100. –9859

Placement Agencies

PRIMARY CARE OPPORTUNITIES: WESTERN US – Primary care physicians needed in rural areas. Combine quality life and quality medicine. Excellent income and benefits. Abundant outdoor activities. Call or send CV: FHS, 4656 S. Utah Ave., Butte, MT 59701; tel (800) 241-8660. –1847

US OPPORTUNITIES-FAMILY PHYSICIANS/ SPECIALISTS: – Choose from solo, group or hospital-based practices. Immediate needs in Texas, California, Georgia, Tennessee, Alabama, Florida, Ohio, New Hampshire, Washington and Idaho. Personal interviews, help with licensure and immigra-

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All of your assignments will be arranged for you, with accommodation and travel expenses paid for by the OMAPS Rural Placement Program.

To qualify as a locum, a physician must be:

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- in possession of an active billing number; or to qualify you must have completed undergraduate or post-graduate training in Ontario;
- a resident of Ontario throughout the duration of the contract;
- a member in good standing of the Canadian Medical Protective Association; and
- certified in Advanced Cardiac Life Support (ACLS) and Advanced Trauma Life Support (ATLS) or willing to obtain certification

To receive an application form or more information about the program, please contact:

June Dyson – Administrator, OMA Placement Service

525 University Avenue, Suite 300, Toronto, Ontario M5G 2K7 (416) 340-2908 or Toll-free 1-800-268-7215 ext. 2908

OMAPS Rural Placement is administered by the Ontario Medical Association with funding assistance provided by the Ontario Ministry of Health.

OMA

–1364

Placement Agencies

tion provided at no cost. Available 24 hours. Contact: Rose Waddell, Medical Staffing Network, tel (800) 608-6626 or (604) 946-2066, or fax CV to (604) 946-0400. –1830

FAMILY PRACTITIONERS: ARIZONA, US – Several very attractive primary care practice opportunities are currently available throughout Arizona and include both private practice and employment options. Obstetrics is potentially available but not required. In addition to offering solid financial and benefit packages physicians will enjoy a sense of practice autonomy. For more information or advice on your eligibility call (800) 991-6661 (toll free) or forward your CV to: Health Search Canada, 148 York St., London, ON, Canada N6A 1A9. –1808

AMERICAN OPENINGS: – 5G-HCR, an American company that specializes in physicians from Canada who wish to relocate to the United States. Qualified family practice physicians are urgently needed. Call us at (518) 481-5845 or (518) 483-0445 or write to: 5G-HCR, 60 Park St., Malone, NY 12953. –1742

US AND CANADIAN OPPORTUNITIES: – In locations of your choice. Health Search Canada offers free private consultation on immigration, licensure, obtaining a billing number, and places to live. At no cost to you we search out opportunities and organize your visit to a place and practice that matches your personal and professional needs. Just forward your CV or contact: Health Search Canada, 148 York St., London, ON N6A 1A9; tel (519) 672-0777 (collect, 24 hours), fax (519) 672-3528. –9958

PRIMARY CARE AND SPECIALTIES: ALABAMA, US – Beautiful state-mountains, rivers, Gulf of Mexico, beaches, warm climate. Most specialties needed, especially primary care. Excellent salary and benefits. Contact: Betty Barfield, PhD, tel (334) 279-1109, fax (334) 272-6351, 6336 Eastwood Glen Pl., Montgomery AL 36117. –9993

Positions Vacant

ANESTHETIST/GP AND GP LOCUM: AB – Required immediately for 10-doctor clinic in Rocky Mountain House, Alberta. Busy practice with hospital privileges and equal on-call schedule. Rocky Mountain House is located 1 hour from Rockies with excellent summer and winter outdoor activities. One hour from Red Deer and 2 hours from Edmonton or Calgary. Contact: Dr. Gordon Brown, (403) 845-3315 (bus.), (403) 845-4935 (res.); fax (403) 845-2177. –1651

EMERGENCY PHYSICIANS: ON – A well-established, congenial group of emergency physicians in Guelph, Ontario is seeking two full-time emergency physicians in order to accommodate expanded group activities commencing in July 1996. Applicants must have emergency training or extensive emergency room experience. Competitive fee-for-service remuneration. Guelph is a progressive, family-oriented community. Single emergency room serves population of 100 000. If interested please send CV to: Guelph Emergency Medical Services, c/o Dr. Ray Galardo, 305-73 Delhi St., Guelph, ON N1E 6L9; tel (519) 837-1401. –1837

FAMILY PRACTICE: AB – Friendly, four-medical-doctor clinic requires locum and/or associate to join modern clinic in growing community. Several local doctors leaving for the States. Local hospital privileges available. City of Spruce Grove, 15 minutes west of Edmonton. Phone Dr. Robinson, (403) 962-9393. –1831

FAMILY PRACTITIONER: AB – The Boyle McCauley Health Centre is a community health centre providing services to a culturally diverse low income population in Edmonton's inner city. It is a registered non-profit organization and has been in operation since 1980. The centre is now seeking a third physician to work as a member of a dynamic multidisciplinary team of doctors, nurse practitioners, LPNs and social workers. Practitioners work closely with the acute referral hospital and the University of Alberta Faculty of Medicine as well as a number of local service agencies and private practice physicians. The team provides a range of primary care, educational, and counselling services within a health promotion framework. This is a full-time contract, salaried position. Candidates wishing to work on a part-time basis will be considered. This competition will remain open until a suitable candidate(s) is/are found. Send CVs to the Boyle McCauley Health Centre, attn: Sharon Thurston, Executive Director, 10628 - 96 St., Edmonton, AB T5H 2J2; fax (403) 422-7343. –1825

GENERAL PRACTITIONER: AB – With anesthetic qualifications and obstetrical experience required for rural practice in Hanna, Alberta. Hanna is centrally located in Region 5 of the Regional Health Authorities recently announced by Alberta Health. The Hanna Health Care Complex (acute care and long-term care) serves a population of 8500 people and geographically encompasses a large area in east-central Alberta. A medical clinic owned and operated by the Hanna Health Care Complex as a society is the only medical clinic in Hanna. It is located immediately adjacent to the

EMERGENCY ATTENDING PHYSICIAN

The Department of Pediatrics and Child Health, University of Manitoba, and the Children's Hospital, Health Sciences Centre is seeking an Emergency Attending Physician for a geographic full-time contingent faculty position at the Assistant Professor level.

The successful candidate will join other physicians in providing clinical care in the emergency department. The Children's Hospital is the major tertiary care facility in Manitoba serving both the medical and surgical needs of the pediatric population of Manitoba. The emergency section has approximately 34 000 patient visits per year.

Candidates must have Senior Specialty qualifications in emergency medicine in the country of current practice and must be eligible for registration with the College of Physicians and Surgeons of Manitoba. Certification in pediatrics by the Royal College of Physicians and Surgeons of Canada is preferred.

In addition to the provision of clinical services, the successful candidate will be responsible for supervision and teaching of both undergraduate and postgraduate trainees within the section.

The university encourages applications from qualified women and men, including members of visible minorities, aboriginal people and persons with disabilities. The university provides a smoke-free work environment, save for specially designated areas. In accordance with Canadian immigration requirements, this advertisement is directed to Canadian citizens and permanent residents. Please apply in writing, including a curriculum vitae and a brief outline of specific interests and goals in both the short and long term, to:

DR. M. TENENBEIN
DIRECTOR, EMERGENCY SERVICES
CE205 CHILDREN'S HOSPITAL
HEALTH SCIENCES CENTRE
840 SHERBROOK STREET
WINNIPEG, MANITOBA R3A 1S1

Closing date for receipt of applications is March 31, 1996.

–1811

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Internet practice@mcimed.com

–6723

Emergency Physician
St. Paul's Hospital, Vancouver, BC

St. Paul's Emergency Associates seeks a full-time emergency physician to join a group of 16 full-time emergency physicians providing emergency services in an urban-core emergency department. St. Paul's Hospital is a 511-bed tertiary/quaternary care facility associated with the University of British Columbia, and is a centre of excellence for cardiac care and HIV-related illness. Emergency physicians treat 55,000 patients annually, and provide 8 hours of triple and 16 hours of double coverage daily. The Department of Emergency Medicine provides training to medical students, residents, physicians and allied professionals, and is the geographical base for the UBC CCFP(EM) program. An active emergency research program has been established and funded. Competitive remuneration is provided through an alternate-payment program and has been structured to reward academic achievement. Clinical duties are scheduled to protect time for non-clinical involvement. A fully-funded sabbatical program is well-established.

The successful applicant will be FRCPC, ABEM, or CCFP(EM) certified, and will have a proven record of excellence in clinical and academic emergency medicine. The group seeks a dynamic team physician who is committed to teaching and research. Those interested should send a CV and personal letter, in confidence, to:

Dr. Jeremy Etherington
Chairman
Department of Emergency Medicine
St. Paul's Hospital
1081 Burrard St.
Vancouver, BC V6Z 1Y6

–1812

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–1844

complex. This association results in very attractive lease options combined with numerous other benefits. There are currently three full-time physicians with full hospital privileges; however, the practice is ideally suited for four physicians. For more information contact the undersigned: Mr. Stan Faupel, Administrator, Hanna Health Care Complex, PO Box 730, Hanna, AB T0J 1P0; tel (403) 854-3331 (hospital) collect. –9873

FAMILY PRACTICE: BC – Long-term locum desired for extended-hours family practice in Kamloops, BC. Friendly, easy-going staff. Young clientele in growing suburban residential area. Excellent remuneration. Opportunity for future buy-in or permanent position. Short-term locum enquiries also welcome. Reply in confidence, tel (604) 851-1326 or Box 729, CMAJ. –1842

FAMILY PHYSICIANS (2): BC – Port Hardy Medical Clinic requires two full-time family physicians to join the practice from June 1, 1996. Busy three-practice office located beside hospital. Obstetric, pediatric, emergency medicine, and trauma care required in shared one-in-five rotation. Northern isolation allowance. Exquisite ocean and forest surround this attractive, well-serviced town of 6000 people with three aboriginal villages nearby. Three-month summer locum also required. Apply with CV to: Port Hardy Medical Clinic, PO Box 1619, Port Hardy, BC V0N 2P0; tel (604) 949-7043, evenings please. –1829

GENERAL PRACTICE: BC – Nanaimo, British Columbia. Busy, well-established clinic requires general practitioner with a view to an associateship. Obstetrics preferred. Close to hospital, lab, x-ray and pharmacy. Computerized office. Pleasant, well organized staff. Reply in confidence to: Box 723, CMAJ. –1803

PHYSICIAN: BC – Vacancy in a busy, unopposed two-physician practice in Logan Lake, BC. Long-term locum/purchase option. Population 2800; 30 minutes from Kamloops; 2 hours from the Okanagan; 3½ hours from Vancouver. Underserviced area - 100% MSP payment plus additional 9.4% northern allowance. Contact: Dr. E. Ries, tel (604) 523-9455, fax (604) 523-9343. –1656

FAMILY PHYSICIAN: BC – One salaried position available for second physician to join family physician currently in 6th year of employment with a First Nation (Nisga'a) Health Board in the beautiful Nass Valley. Physician will provide outpatient clinics and on-call emergency services in a modern, well-equipped diagnostic and treatment centre in New Aiyansh. No obstetrics. Support staff includes three nurses, psychologist, physiotherapist, dentist, and community health representatives. Patients are predominantly aboriginal — friendly and welcoming to medical staff. Ability to work in a team setting and report to a community board is required. Family accommodations will be made available. Generous fringe benefits, including pension plan and extended health plan. Relocation costs and expenses related to job interviews provided. Flexibility and ability to work in a challenging and evolving work setting essential. For further information including detailed job description, salary range, and information about the Nass Valley, please contact: Mr. Reginald Percival, Executive Director, Nisga'a Valley Health Board, PO Box 234, New Aiyansh, BC V0J 1A0; tel (604) 633-2212, fax (604) 633-2512. –9008

FAMILY PRACTICE OPPORTUNITY: ON – Immediate family practice oportunity in Toronto. Establish your own busy practice in an efficiently administered clinic. No start-up headaches, no investment required. Part time or full time. Contact Pat Fuller, tel (416) 256-4113. –1846

FAMILY PHYSICIANS

Become part of a multidisciplinary health care team in aboriginal health care on a university team.
J.A. Hildes Northern Medical Unit has full-time and locum family practice positions available in northern Manitoba and the Keewatin District of the Northwest Territories.
Compensation: up to $13 500 per month. Benefits include vacation and education leave, moving expenses and subsidized housing.
Enquiries: **Michelle Vandenbroeck**
J.A. Hildes Northern Medical Unit
Department of Community Health Sciences
T162-770 Bannatyne Avenue
Winnipeg, Manitoba R3E 0W3
Tel (204) 789-3711 (collect)
Fax (204) 774-8919 –1735

GENERAL PRACTITIONER: ON – To replace physician in established practice in ValCaron, 20 minutes from Sudbury, with multispecialty backup. Eligible for underserviced area grant. On call 1 in 12 available. Fully equipped office, experienced staff. No starting cost. Call (705) 671-2855 (evgs.). –1834

FAMILY PRACTICE: ON – Lindsay, Ontario. Busy practice, lovely town, excellent recreational facilities, 1 hour from Toronto. Modern computerized office sharing space with two general practitioners. Above-average income. 120-bed hospital with all specialists. Obstetrics and emergency room optional. Tel (705) 423-0433. –1826

PHYSICIAN: ON – Busy, two-physician rural practice requires a well-rounded physician to join practice. Obstetrics and emergency coverage required. Forty km to Kitchener, Waterloo, Guelph. Privileges available in 35-bed rural hospital. Ministry Emergency Sessional Payment Program in place. Contact: Ms. Brenda Camplin, Drayton Community Health Centre, 62 Wood St., Drayton, ON N0G 1P0; tel (519) 638-3088, fax (519) 638-3982. –1821

FAMILY PHYSICIAN: ON – High-gross established practice in new medical building with lab, x-ray and pharmacy in St. Thomas, 20 minutes to London. On call 1 in 15. Obstetrics and emergency optional. Walk-in shifts available. Local hospital privileges; excellent specialist backup. Physician relocation to US. Flexible start date. Let's talk. Reply evgs./weekends, tel (519) 679-1956, fax (519) 679-0914. –1819

FAMILY PRACTICE: ON – The Fort William Clinic, a 19-doctor multispecialty group is accepting applications for family practitioners or locum tenens. Enjoy an active practice with hospital privileges. Emergency and obstetrics optional, but encouraged. Thunder Bay is a community of 120 000 with exceptional recreational opportunities ranging from hunting and fishing, to skiing and sailing. Involvement with teaching medical students and residents in the Northwestern Ontario Medical Program/Family Medicine North is also supported. Please call collect, Dr. R. Almond or Executive Director at (807) 626-1218, or write to: Fort William Clinic, 117 S McKellar St., Thunder Bay, ON P7E 1H5. –1818

CRITICAL CARE CLINICAL ASSISTANTS: ON – Hamilton, Ontario. Full-time and part-time positions available in tertiary care intensive care units. Applicants must have Ontario Certificate of Independent Practice, CMPA, ACLS. Critical care experience preferred. Letter of application with CV to: Dr. C. Hamielec, Rm 3U3, 1200 Main St. W, Hamilton, ON L8N 3Z5. Tel (905) 521-2100, ext. 6218 or fax (905) 521-5053. –1806

FAMILY PHYSICIANS: ON – Bruce Peninsula beckons family physicians - Wiarton, Ontario offers the small town or rural lifestyle that you have been looking for! Sailing, flying, cross-country skiing, swimming and hiking on the world famous Bruce Trail are all at your doorstep. Our 7200-person catchment area, augmented by a very large summer tourist population, offers the full scope of family practice with a new 34-bed hospital adjacent to doctors' offices. Referral services are available within 1 hour. Shared emergency call with five family physicians. ACLS required. Obstetrics optional. Contact the Executive Director, Bruce Peninsula Health Services, tel (519) 534-1260. –1800

FAMILY PHYSICIANS: ON – Wanted to join busy practice in thriving community approximately 40 minutes north of Toronto. Fully outfitted clinic with lab, x-ray, optometrist, pharmacy, drugstore and dentist. Approximately 2000:1 patient doctor ratio. Low overhead. Plus, many new homes are scheduled for construction in the immediate area. Lovely lakeside location that offers an abundance of leisure activities. Must be licensed to practise in Ontario. Please reply to: Mr. Paul McVeigh, tel (905) 477-8000, ext. 233 or Mrs. E. Jeffrey, tel (905) 476-3771. –1771

FAMILY PHYSICIANS: ON – Minden, Ontario. Family physicians required for this picturesque, cottage-country village, 2.5 hours from Toronto. The service area has double the provincial average of seniors, an emergency services facility and a 60-bed LTC unit. The provincial government has approved a $10.6 million capital expenditure for the area. Excellent elementary school and numerous four-season recreational opportunities, all in a clean, safe rural setting. Strong community support exists for physicians interested in making Minden their home. For more information write: The Community Committee for Physicians, PO Box 359, Minden ON K0M 2K0; or contact: Reeve Jeanne Anthon, tel (705) 286-1260, (705) 286-3756 (evgs.); chairman Jack Brezina, tel (705) 286-1288 or (705) 286-1958 (evgs.); or Foster Loucks, Executive Director, Health Services Board, tel (705) 286-4997. –1721

FAMILY PHYSICIAN: ON – Establish your family practice with our four-doctor group in a new office in the picturesque, progressive and growing town of Tillsonburg, population 13 000; 40 minutes to London, 90 minutes from Toronto. For further information tel (519) 842-3636 (bus.), fax (519) 842-9522 or reply to: Dr. Andrew, Gateway Health Centre, 594 Broadway Ave., Tillsonburg, ON N4G 5K9. –1709

FAMILY PHYSICIAN: ON – To join group practice in Sydenham, lakeside village a short drive north of Kingston and Queen's University. Modern office, congenial group. Great recreational area. Contact: Dr. Nancy Carr, tel (613) 376-3389 (evgs.). –1642

FAMILY PHYSICIANS: ON – With or without anesthesia are needed to work with a nine-doctor group in beautiful northwestern Ontario. If the thought of pursuing activities such as skiing, fishing, sailing, and hunting without having to go far from your home is of interest to you, call us. If the thought of working in a modern clinic adjacent to a fully accredited hospital with a 1-in-13 call rota is of interest to you, call us. Dryden is a full service community for an area population of 15 000 with excellent educational and recreational activities. Lucrative financial incentives for a GP/anesthetist are available. Call Dr. Mark Dahmer at (807) 223-4202 (after 6 pm) or Nancy Pentney at (807) 223-2260 (during office hours). –9006

GROUP PRACTICE: ON – London; well-established and thriving family practice of four, seeks physician(s) who desires to work in a team environment with other physicians, registered nurses and support staff. We are centrally located in a new building and with no start-up costs this makes for a good place to practise medicine. If you've read this

far, you have an interest, so call (519) 673-5985 (days), or (519) 433-9864 (evgs./weekends). –9998

PHYSICIAN: ON – Join a small, busy medical practice in unspoiled northwestern Ontario. Call one in twelve at fully equipped, 67-bed hospital. Enjoy fishing, sailing, skiing, hockey, boating, hiking, snow-machining, golfing, biking, camping and hunting amongst pristine rivers, lakes and forests. Friendly town of 7000, with excellent recreational, educational and cultural facilities. Contact Dr. Michael A. Cortens; tel (807) 223-2286, fax (807) 223-7282. –9994

ASSOCIATESHIP FOR BUSY PRACTICES: ON – For takeover or associateship in downtown Toronto and London locations. Tel Kevin MacLeod at (416) 360-7311. –9990

PHYSICIANS: ON – Required for (a) locum, (b) part-time, (c) after hours. Prime location, excellent working conditions. Guaranteed minimum. Contact: Laura, tel (905) 336-1221 (bus.) or Gina, tel (905) 567-7393 (res.). –9989

FAMILY PRACTICE: ON – Brampton, Ontario. Busy family practice office in growing area seeking full or part-time associate. Obstetrics, emergency and other hospital work optional, but available in nearby Peel Memorial Hospital. Contact: Dr. Paul Carabott, tel (905) 792-2245. –9951

FAMILY PHYSICIAN / GENERAL PRACTITIONER: ON – One full-time and one part-time associate required (to replace one doctor leaving) to join busy three-doctor cottage country practice in Northbrook, Ontario, a growing area. No hospital work or obstetrics necessary. No call. Expenses 29%. New modern clinic. Call Dr. Tobia, (613) 336-8888 (days), (613) 336-9430 (after hours). –9940

ASSOCIATES (2): SK – Two associates required in a well-established practice in the city of Regina, Saskatchewan; one to replace a retiring female physician. Three major hospitals in the city. Easy terms. Clinic works on appointment system only. Reply to: Box 722, CMAJ. –1765

FAMILY PRACTICE: SK – Immediate full/part-time positions available for two physicians at extended-hours medical clinics in Regina. Flexible hours. Minimum guaranteed income $5000 per month. Clinics equipped with lab and x-ray. Contact: Dr. A. Virjee, tel (306) 584-3833, (306) 775-2688, fax CV to (306) 585-3833. –9002

FAMILY PHYSICIANS

Northern Medical Services, University of Saskatchewan has salaried positions available in remote areas of northern Saskatchewan. Health care is delivered from modern facilities by teams of physicians, nurses, community health care representatives and visiting consultants.
Salary range: $97 617-$114 699 per annum. Additional benefits: subsidized modern furnished housing and utilities; transportation expenses; and paid leave for 4 weeks of vacation, 4 weeks of continuing education and two conferences per year.
To apply, or for further information contact:

Wayne Nelson, Administrative Officer
Northern Medical Services
102, 308 - 4th Ave. N.
Saskatoon, SK S7K 2L7
Fax (306) 665-6077 –9714

FAMILY PRACTITIONERS: OHIO, US – Great opportunity to join two other happy Ontario physicians in Bellefontaine, Ohio (1 hour from Columbus). Excellent hospital and specialist support. Opportunity to teach if desired. Nice lifestyle, growing community, good schools, 43 000 + service area. Great salary, benefits and working conditions. No managed care. The best decision you will ever make. Call Dr. Boyd Hoddinott at (513) 592-3808 or fax your CV to (513) 592-8633. –1845

FAMILY PRACTICE: US – US $160 000 financial package. Live on the largest man-made lake in the US; seven shopping malls and eight major universities within 2 hours. This practice has minimal managed care and lowest malpractice in the state. No practice management in this hospital-owned clinic. You can enjoy higher compensation, more time with your family, lower taxes, less government control of your practice. Be appreciated as a physician and be an easy drive from Ontario. All interview, immigration and relocation expenses paid. Call Joe Woods at (800) 347-7987, ext. 5-422, or mail your CV to his attention at Harris Kovacs Alderman, 4170 Ashford-Dunwoody Rd., Ste. 500, Atlanta, GA 30319. You may also fax your CV to him at (800) 254-8233. –1836

INTERNIST: ON – A southern Ontario specialist group needs an internist. Preferred candidates will have special interest and training in endocrinology. Interested parties please reply to: D. Dabreo, MB, BS, FRCPC, fax (519) 752-2469. –1824

INTERNIST OR PEDIATRICIAN: ON – Interested in allergy/respirology required for referred only practice in west Toronto. May be part time or full time. This is an excellent practice with above-average income. Eventual purchase possible. Reply to: Box 725, CMAJ. –1805

GENERAL INTERNIST: ON – To join a group of nine family physicians in magnificent northwestern Ontario. Style of practice tailored to your wishes. State-of-the-art stress testing and endoscopy equipment, and more! Underserviced area grant available. Call Nancy Pentney at (807) 223-2260 (days) or Mark Dahmer at (807) 223-4202 (evgs.). –9997

INTERNAL MEDICINE: VIRGINIA, US – Sterling: a board-certified internist and a graduate of Memorial University is seeking a BC/BE general internist to join our staff. Excellent benefit package includes competitive salary package, malpractice protection, 3 weeks paid vacation including CME, disability, buy-in option and retirement plan. Excellent suburban community 45 minutes west of Washington, DC, with excellent schools, cultural and recreational activities. Please direct responses or enquiries to: Grace L. Keenan, MD, President, Nova Medical Group, Inc., 21036 Triple Seven Rd., Sterling, VA 20165; tel (703) 430-4343, fax (703) 430-9585. –9992

NEPHROLOGISTS (2): BC – The Division of Nephrology, Department of Medicine at the University of British Columbia invites applications for two nephrologists at the clinical assistant professor or clinical instructor level. These are 1-year renewable appointments. Candidates will be expected to have proficiency in all clinical aspects of nephrology, dialysis and transplantation, to have demonstrated teaching ability at both the undergraduate and postgraduate levels and to have experience in clinical investigation. Candidates are expected to participate in all clinical and academic activities of the division. Successful applicants will be located at one of the UBC teaching hospitals in a large nephrology program. The successful candidate will have an FRCPC or equivalent in nephrology and must be eligible for licensure in the province of British Columbia. Please submit a letter of application, CV, a statement of areas of expertise and strengths and the names of three referees, no later than Mar. 30, 1996, to: Dr. E.C. Cameron, Division Head, Department of Medicine, University of British Columbia, Vancouver Hospital Health Sciences Center, 320-575 W 8th Ave., Vancouver, BC V5Z 1C6. Salary will be commensurate with qualifications and experience. Preferred start date is July 1, 1996. In accordance with Canadian immigration requirements, this advertisement is directed to Canadian citizens and permanent residents. UBC welcomes all qualified applicants, especially women, aboriginal people, visible minorities and persons with disabilities. –1832

NEPHROLOGIST: US – One-hundred-and-forty-five-physician multispeciality group seeking a second BC/BE nephrologist in a 100% nephrology practice. Teaching and/or research are readily available in affiliation with a university school of medicine. Upper midwest US city of 55 000 with a variety of cultural and recreational activities. Contact: Charles Matenaer, tel (800) 611-2777. –1849

NEURORADIOLOGIST: SK – The College of Medicine, University of Saskatchewan and the Saskatchewan District Health Board at the Royal University Hospital invite applications for the position of an academic neuroradiologist within the academic department of medical imaging. Advanced training in all aspects of neuroradiology is a requirement, as is certification or eligibility for certification with the Royal College of Physicians and Surgeons of Canada. The candidate would have major responsibility for teaching and development of the neuroradiology program. This position has been cleared for advertising at the two-tier level. Applications are invited from qualified individuals, regardless of their immigration status in Canada. The University of Saskatchewan is committed to the principles of employment equity and welcomes applications from all qualified candidates. Women, people of aboriginal descent, members of visible minorities, and people with disabilities are invited to identify themselves as members of these designated groups on their applications. Please forward your letter of application and resume to: Dr. J. Loewy, Academic Head, Department of Medical Imaging, Royal University Hospital, 103 Hospital Dr.. Saskatoon, SK, Canada S7N 0W8. –1833

DIVISION HEAD, NUCLEAR MEDICINE: ON – The Department of Radiology invites applications for the above post at the Toronto Hospital, Toronto, Ontario, Canada. The department is a major teaching facility of the University of Toronto and the Nuclear Medicine Division is equipped with 12 gamma cameras performing 2500 examinations per year including general nuclear medicine and cardiac nuclear medicine. It is an approved site for radio-nuclide preparation and is upgrading its facilities. The department has two clinical sites: one at the Toronto General and the other at the Toronto Western. The division head is responsible for providing clinical service, research, undergraduate and postgraduate teaching. The successful candidate is required to have fellowship qualifications (FRCPC or equivalent) in nuclear medicine and diagnostic radiology and is expected to have a history of peer-reviewed funded research and publications. Previous experience in administration, PET scanning and nuclear cardiology is an asset. Salary will be commensurate with experience. In accordance with employment and immigration regulations, Canadian citizens and permanent residents of Canada will be given priority. Please send curriculum vitae to: Dr. C.S. Ho, Department of Radiology, The Toronto Hospital, 585 University Ave., Toronto, ON, Canada M5G 2C4. –1820

OTOLARYNGOLOGIST: BC – Royal Inland Hospital, Kamloops, B.C. Interior British Columbia city is recruiting an otolaryngologist to practise general otolaryngology within facilities of a regional referral hospital. The community has experienced full otolaryngologic service in the past and is looking for an additional otolaryngologist. The majority of ancillary surgical specialties are represented. Investigation modalities are available including CT scan, MRI, polysomnography, brainstem evoked audiometry, endoscopic sinus surgery and outpatient ambulatory care surgical service. The community

COMMUNITY SURGEON

The Lennox and Addington County General Hospital is located in Napanee, Ontario and serves a population of 35 000 people. Napanee is centrally located mid-way between Toronto and Montreal. It is a great outdoor recreation area and has excellent schools.

We enjoy a superbly equipped and expanding surgical unit. The medical community is stable, congenial and is committed to excellence in its provision of care. The hospital is a teaching unit of Queen's University and a suitable candidate will be offered an academic appointment with the university.

We require an FRCSC in general surgery with a breadth of skills appropriate to a smaller community setting. Caesarean section ability is required.

Reply in writing, enclosing your curriculum vitae, to:

Glenn D. Brown, MD
Chief of Staff
Lennox and Addington County General Hospital
8 Park Drive
Napanee, ON K7R 2Z4

–1809

ROSS MEMORIAL HOSPITAL

GENERAL SURGEON

ROSS MEMORIAL HOSPITAL

This 206-bed community hospital in Lindsay announces that there is an opportunity within its general surgical staff.

Enjoy quality of life, recreational haven, excellent schools, in an active community 90 minutes from Toronto. Operative obstetrical skills are desirable.

Please direct resumes or enquiries to:

Chief of Surgery
Chief of Staff or
Chair of the Search Committee
Ross Memorial Hospital
10 Angeline Street North
Lindsay, Ontario K9V 4M8
Tel (705) 324-6111

–1699

University of Alberta
Edmonton

Director of Division of Cardiology,

Department of Medicine

Applications are invited for the position of Director, Division of Cardiology, Department of Medicine at the University of Alberta. The Division currently consists of 13 geographic full time cardiologists located at the University of Alberta Hospital site, with a full range of sub-specialties and diagnostic and therapeutic services. A similar number of part-time clinical faculty in cardiology exist in the region and an active cardiovascular surgical division is present on site, including a cardiac transplantation program. Successful cardiovascular research programs exist in fundamental, clinical and community based research and there is a fully approved postgraduate educational program in cardiology. Significant opportunities to recruit exist and are facilitated by the support of the Alberta Heritage Foundation for Medical Research. Interested applicants should hold an MD and fellowship in the Royal College of Physicians and Surgeons of Canada in Cardiology or equivalent and have demonstrated leadership and clinical expertise along with scholarly accomplishment in research and teaching.

Academic rank and remuneration for this senior position will be commensurate with qualifications and experience. Deadline for applications is 1 May 1996. Please send curriculum vitae and the names and addresses of three references to:

Dr. P.W. Armstrong
Chair, Department of Medicine
2F1.30 Walter C. Mackenzie Health Sciences Centre
University of Alberta
Edmonton, Alberta, Canada, T6G 2R7

The University of Alberta is committed to the principle of equity in employment. As an employer we welcome diversity in the workplace and encourage applications from all qualified women and men, including Aboriginal peoples, persons with disabilities, and members of visible minorities.

–1816

POSITIONS VACANT

boasts excellent quality of life for anyone interested in outdoor activities in all seasons. Call coverage sharing is available. Subspecialty otolaryngology expertise is available within 3-1/2 hours road surface travel time. Training to practise general otolaryngology is required. Interested applicants may contact: The Medical Director, Royal Inland Hospital, Kamloops, BC V2C 2T1; tel (604) 374-5111, local 773. –1782

PALLIATIVE CARE PHYSICIANS, HALF TIME: ON – Community palliative care physicians wanted to join an established palliative care program. Some past experience with palliative care is required, however the program is willing to train those who do not have extensive experience. Call is shared between team members and there are weekly patient care and educational rounds. This is an opportunity to work with a multidisciplinary palliative care team comprised of home palliative care, inpatient consultation service, out-patient clinics and a specialty palliative care unit. The program is affiliated with a major teaching hospital and thus includes a hospital and university appointment. Remuneration is fee for service with a monthly supplement. This is a chance to be involved in a rapidly evolving discipline, with a supportive, enthusiastic group of caring colleagues in an academic environment. CCFP or FRCPC, and a licence to practise in Ontario are required. Reply with CV in writing, to: Dr. M.A. Huggins, Director, Palliative Medicine, The Toronto Hospital, 200 Elizabeth St., M/LW 2-033, Toronto, ON M5G 2C4; fax (416) 340-3220. –1799

PEDIATRIC PRACTICE: NB – Fredericton, New Brunswick. General consulting pediatrician required to join established group of five pediatricians in Fredericton, N.B. Modern 450-bed hospital with group sign-out arrangement. Modified level III neonatal NICU with full-time neonatologist. One night in four/five call. Residents from Dalhousie University provide in-house coverage. Contact: Dr. Colin Gaston, tel (506) 458-0283 or (506) 459-8948. –1796

RADIOLOGIST: BC – A permanent and/or locum radiologist is required for Prince Rupert Regional Hospital, a 71-bed (48 acute care and 23 extended care) regional hospital serving Prince Rupert and surrounding area. Prince Rupert is a west coast city of approximately 20 000 that has a temperate climate and excellent recreational and cultural amenities. The department serves the Pacific Northwest with state-of-the-art equipment, including a Siemens S1450 Doppler capable ultrasound, Siemens Remote R&F, G.E. Advantx DRS Digital R&F and Picker Sureview Mammography Unit. The working conditions are excellent and the atmosphere congenial. To be considered for this position, a candidate must have obtained his/her LMCC status and have a fellowship in radiology with experience in ultrasound. Total number of examinations per year is approximately 20 000. Fee-for-service basis. Please submit, in confidence, a curriculum vitae and references to: Dr. R. Attisha, Chief of Staff, Prince Rupert Regional Hospital, 1305 Summit Ave., Prince Rupert, BC V8J 2A6; fax (604) 624-2195, tel (604) 624-0233. –9943

FULL-TIME RADIOLOGIST: ON – Busy hospital-based group with all modalities except MR (approval pending) requires the services of an eighth radiologist. Additional training in nuclear medicine, mammography or pediatric radiology would be an asset. Very competitive income assured to successful applicant. Preference and appropriate additional remuneration would be given to an applicant with FRCPC in nuclear medicine as well as radiology. Please apply with CV to: Dr. Sam Lam, Chief, Department of Diagnostic Imaging, Peel Memorial Hospital, 20 Lynch St., Brampton, ON L6W 2Z8; tel (905) 796-4085. –1773

RADIOLOGIST: ON – Applications are invited for director of MRI services with experience in neuro-MRI to join a group of eight radiologists in a busy community hospital. The candidate, in addition to MRI responsibilities, will be expected to participate in general radiological work. We have spiral CT, interventional angiography, digital fluoroscopy, mammography and ultrasound with colour flow doppler. MRI proposal submitted to the ministry. The position will be available pending ministry approval. Please reply to: Dr. Afsal Ahmad, Director of Diagnostic Imaging, The Mississauga Hospital, 100 Queensway W, Mississauga, ON L5B 1B8; tel (905) 848-7539. –1840

RADIOLOGIST: ON – Established diagnostic imaging facility looking for a dedicated, congenial radiologist. Flexible work schedule, exceptional income, long holidays, with no call, or weekends. Applications are invited from interested candidates licensed to practise in Ontario. Reply to: Box 660, CMAJ. –9970

GENERAL SURGEON: ON – Required July 1, 1996 to replace solo surgeon in Dunnville, a rural and progressive, stable community of 15 000 in central-western Ontario. Picturesque Dunnville offers a relaxing, safe, community-oriented lifestyle for individuals and families. Recreational activities offered include a nine-hole golf course, fishing, boating, camping and swimming. Dunnville is located on the banks of the Grand River just minutes from Lake Erie. The hospital is a fully accredited facility of 41 acute and 24 long-term-care beds with

PEDIATRIC INTENSIVE CARE PHYSICIAN

The Department of Pediatrics and Child Health, University of Manitoba, and the Children's Hospital, Health Science Centre is seeking a fourth Pediatric Intensive Care Physician as a geographic full-time contingent faculty physician at the Assistant/Associate Professor level. The PICU is a tertiary level, 13-bed unit caring for a wide variety of medical and surgical critical pediatric illnesses.

Qualifications include successful completion of fellowship training in pediatrics, anesthesia or pediatric surgery. In addition, the successful candidate will have 1 to 2 years training in a pediatric critical care fellowship program and have demonstrated excellence in performing clinical duties and teaching unit-based residents and nurses. Strong interpersonal skills, commitment to the care of children and families and interest in outreach educational programs or research are necessary.

Candidates must have Senior Specialty qualifications in the country of current practice and must be eligible for registration with the College of Physicians and Surgeons of Manitoba. Certification by the Royal College of Physicians and Surgeons of Canada is preferred.

The university encourages applications from qualified women and men, including members of visible minorities, aboriginal people and persons with disabilities. The university provides a smoke-free environment, save for specially designated areas. In accordance with Canadian immigration requirements, this advertisement is directed to Canadian citizens and permanent residents. Please apply in writing, including a curriculum vitae and a brief outline of specific interests and goals in both the short and long term, to:

DR. M. KESSELMAN
DIRECTOR
PEDIATRIC INTENSIVE CARE UNIT, AE 203
820 SHERBROOK STREET
WINNIPEG, MANITOBA R3A 1R9

Closing date for receipt of applications is March 31, 1996. –1810

PROFESSOR AND CHAIR DISCIPLINE OF PEDIATRICS

Memorial University of Newfoundland invites applications for the position of Professor and Chair of Pediatrics. This is the senior academic appointment in the discipline, and is a joint appointment of Memorial University of Newfoundland and the Health Care Corporation of St. John's, and is available September 1, 1996.

The discipline includes a fully accredited Royal College of Physicians and Surgeons of Canada pediatric specialty education program, state-of-the-art research facilities for pediatric medicine, research interests in neonatal health care and participation in the faculty's undergraduate and graduate studies programs.

The successful candidate will be the academic and clinical leader of the university discipline of pediatrics. This is a major academic position with clinical resources at the Dr. Charles A. Janeway Child Health Centre Site, Health Care Corporation of St. John's. Therefore, applicants should have senior academic experience with proven teaching ability and research interests. Certification in pediatrics from the Royal College of Physicians and Surgeons of Canada is a requirement and the individual must be fully licensable in the province of Newfoundland and Labrador.

In accordance with Canadian immigration requirements, this advertisement is directed towards Canadian citizens and permanent residents of Canada. Memorial University is committed to employment equity.

Interested persons should direct their enquiries and/or applications on or before March 31, 1996 to:

Francis G. King, MD, FRCPC
Professor and Chair
Discipline of Anesthesia
Chair, Pediatric Search Committee
Memorial University of Newfoundland
St. John's, NF, Canada A1B 3V6

–1838

CRITICAL CARE AND RESPIROLOGY

Queen's University, Department of Medicine, invites applications for a geographic full-time academic appointment. Applicants should be certified in internal medicine by the Royal College of Physicians and Surgeons of Canada, hold a certificate of competence in respiratory diseases, and have recognized training in critical care medicine. The candidate will be proficient in critical care and respiratory-related procedures and will be expected to contribute to the Critical Care and Respiratory Diseases Training Programs. Preference will be given to individuals with research training in critical care or the health services area.

In accordance with Canadian immigration requirements, this advertisement is directed to Canadian citizens and permanent residents. Queen's University has an employment equity program, welcomes diversity in the workplace and encourages applications from all qualified candidates, including women, aboriginal people, people with disabilities and visible minorities.

Please submit letter of application, *curriculum vitae* and names of three referees, to:

Dr. P.W. Munt
Head, Department of Medicine
Queen's University
Kingston, Ontario, Canada K7L 3N6
Tel (613) 545-6327
Fax (613) 545-6695

–1839

General Pathologist

Wellness focused health in partnership with individuals and community; promoting dignity and independence.

The Bonnyville Health Centre has an opportunity for a second pathologist to join its team. In cooperation with the Laboratory Director, you will participate in a full service regional program based in the Regional Laboratory in Bonnyville, Alberta. The ideal candidate will hold a fellowship in general pathology, qualify for Alberta licensure,and have an interest in all aspects of general pathology.

The Bonnyville Health Centre is located in the northeast section of the Lakeland Regional Health Authority, one of Alberta's 17 newly formed health regions. The regional population is 169,000, covering a geographical area of 33,000 square miles.

Salary/Contract and benefits are excellent, and you will enjoy practising in a grassroots setting within an easy drive of Edmonton, the provincial capital. Interested applicants should apply to:

LAKELAND Regional Health Authority

Dr. Robert Davey
Laboratory Director
Bonnyville Health Centre
Postal Bag 1008
Bonnyville, Alberta T9N 2J7
Tel: (403) 826-3311

–1531

OBSTETRICIAN/GYNECOLOGIST

The Red Deer Regional Hospital Centre has an immediate vacancy for an Obstetrician/Gynecologist.

The applicant must hold a fellowship in Obstetrics/Gynecology from the Royal College of Physicians and Surgeons of Canada.

The Centre has a departmentalized active medical staff of 122 Physicians. There are four Obstetricians/Gynecologists. Approximately 1800 deliveries are performed annually.

The Red Deer Regional Hospital Centre is a 727 bed multi-institutional facility, providing both acute (339 beds) and long term care (388 beds) to Central Alberta. The Centre serves the 60,000 residents of the city of Red Deer, and a catchment area with a population of approximately 170,000.

Red Deer is situated mid-way between Calgary and Edmonton in the centre of the parkland area. It has a beautiful setting nestled along the banks of the Red Deer River. The city is a progressive, dynamic community with excellent recreational, cultural and educational facilities.

Application forms can be obtained by writing to:

D H R
David Thompson Health Region

Dr. J.A. Ordman, Medical Director
David Thompson Health Region
P.O. Bag 5030
Red Deer, Alberta, T4N 6R2
Tel: (403) 343-4519
Fax: (403) 343-4807

–1817

Positions Vacant

full obstetrical service. It is supported by our congenial medical staff from the service area including three general practitioner anesthetists. For further information, please contact: P.L. Mailloux, Chief Executive Officer, Haldimand War Memorial Hospital, 206 John St., Dunnville, ON N1A 2P7; tel (905) 774-7431, ext. 211, fax (905) 774-6776. –9009

GENERAL SURGEON: ON – Southern Ontario, serving 60 000 population. Above-average income and lifestyle. Endoscopy skills essential. Reply in confidence to: Box 727, CMAJ. –1822

GENERAL SURGEON: ON – To replace a retiring physician in Orangeville, a growing community of 20 000 with a catchment area of 55 000. Less than 1 hour from metropolitan Toronto in a scenic area with many recreational opportunities. A new 108-bed hospital is under construction to be opened the spring of 1997. Share call with two other general surgeons - enjoy excellent support of other local specialists and close working relationships with other regional and tertiary care centres. To explore this attractive opportunity to work in an innovative hospital which recently received a 4-year award with distinction from Accreditation Council, please contact Dr. D. Scott, tel (519) 941-0700 or Dr. H. Bergen, tel (519) 941-8357. –1736

GENERAL SURGEON

South Muskoka Memorial Hospital, Bracebridge, Ontario, wishes to recruit a general surgeon due to a retirement. South Muskoka Memorial Hospital is an 80 bed acute hospital with 30 active medical staff. The catchment population is 25 000 in winter and 80 000 in summer. Bracebridge itself has a population of 12 000 and offers excellent recreational services. Bracebridge is located 200 km north of Toronto where a wide range of arts, entertainment and fine dining are located.

The on-call is shared 1:4 with a second local surgeon (below) and two surgeons 30 minutes away. The hospital is friendly and well equipped.

Contact: **Dr. James Campbell**
PO Box 1424
Bracebridge, ON P1L 1V5
Tel (705) 645-4404 –1848

ORTHOPEDIC SURGEON: ON – Required for progressive, busy 90-bed hospital in pleasant, southwestern Ontario town. Solid industrial/agricultural base. Serving stable area - population 25 000. Income above provincial average. C-arm, arthroscope, total-joint facility available. Excellent internist backup with invasive monitoring, modern five-bed ICU. Full-time radiology and obstetrics/gynecology, general surgery, urology and endoscopy. Five GP/anesthetists provide 24-hour coverage. Enjoy life in a friendly, small town. Ample boating and fishing opportunities. Close to metropolitan centres. Reply to: Box 596, CMAJ. –9930

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FAMILY PRACTICE: BC – Very busy practice for sale in the sunny BC interior, by general practitioner who is relocating. Young clientele for this extended hours family practice set in a rapidly growing area of Kamloops, BC. Gross billings over $210 000 - could easily expand. Lots of new obstetrics, but not necessary. Shared overhead (about 30% of gross) and coverage with two other family physicians. Excellent specialist backup and large modern hospital nearby. Kamloops offers easygoing, safe environment with economic stability and great climate. Lakes and fantastic skiing just 40 minutes. Reply in confidence, tel (604) 851-1326 or to Box 728, CMAJ. –1841

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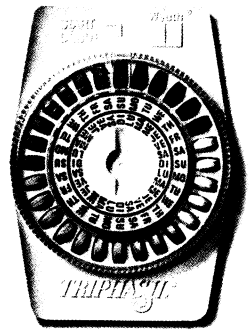

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